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[Continued on next page]

(54) Title: PEPTIDES AND RELATED MOLECULES THAT BIND TO TALL-1

$a^1a^2a^3CDa^6La^8a^9a^{10}Ca^{12}a^{13}a^{14}$

(SEQ. ID. NO: 100),

$b^1b^2b^3Cb^5b^6Db^8Lb^{10}b^{11}b^{12}b^{13}b^{14}Cb^{16}b^{17}b^{18}$

(SEQ. ID. NO: 104)

$c^1c^2c^3Cc^5Dc^7Lc^9c^{10}c^{11}c^{12}c^{13}c^{14}Cc^{16}c^{17}c^{18}$

(SEQ. ID. NO: 105)

$d^1d^2d^3Cd^5d^6d^7WDd^{10}Ld^{13}d^{14}d^{15}Cd^{16}d^{17}d^{18}$

(SEQ. ID. NO: 106)

$e^1e^2e^3Ce^5e^6e^7De^9Le^{11}Ke^{13}Ce^{15}e^{16}e^{17}e^{18}$

(SEQ. ID. NO: 107)

$f^1f^2f^3Kf^5Df^7Lf^9f^{10}Qf^{12}f^{13}f^{14}$

(SEQ. ID NO: 109)

$(X^1)_a$-V^1-$(X^2)_b$ (I)

(57) Abstract: The present invention concerns therapeutic agents that modulate the activity of TALL-1. In accordance with the present invention, modulators of TALL-1 may comprise an amino acid sequence Dz^2Lz^4 wherein z^2 is an amino acid residue and z^4 is threonyl or isoleucyl. Exemplary molecules comprise a sequence of the formulae $a^1a^2a^3CDa^6La^8a^9a^{10}Ca^{12}a^{13}a^{14}$ (SEQ.ID.NO:100), $b^1b^2b^3Cb^5b^6Db^8Lb^{10}b^{11}b^{12}b^{13}b^{14}Cb^{16}b^{17}b^{18}$ (SEQ.ID.NO:104) $c^1c^2c^3Cc^5Dc^7Lc^9c^{10}c^{11}c^{12}c^{13}c^{14}Cc^{16}c^{17}c^{18}$ (SEQ.ID.NO:105) $d^1d^2d^3Cd^5d^6d^7WDd^{10}Ld^{13}d^{14}d^{15}Cd^{16}d^{17}d^{18}$ (SEQ.ID.NO:106) $e^1e^2e^3Ce^5e^6e^7De^9Le^{11}Ke^{13}Ce^{15}e^{16}e^{17}e^{18}$ (SEQ.ID.NO:107) $f^1f^2f^3Kf^5Df^7Lf^9f^{10}Qf^{12}f^{13}f^{14}$ (SEQ.ID NO:109) wherein the substituents are as defined in the specification. The invention further comprises compositions of matter of the formula $(X^1)_a$-V^1-$(X^2)_b$ wherein V^1 is a vehicle that is covalently attached to one or more of the above TALL-1 modulating compositions of matter. The vehicle and the TALL-1 modulating composition of matter may be linked through the N- or C-terminus of the TALL-1 modulating portion. The preferred vehicle is an Fc domain, and the preferred Fc domain is an IgG Fc domain.

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PEPTIDES AND RELATED MOLECULES THAT BIND TO TALL-1

This application is related to U.S. provisional application no. 60/290,196, filed May 11, 2001, which is hereby incorporated by reference.

Background of the Invention

After years of study in necrosis of tumors, tumor necrosis factors (TNFs) α and β were finally cloned in 1984. The ensuing years witnessed the emergence of a superfamily of TNF cytokines, including fas ligand (FasL), CD27 ligand (CD27L), CD30 ligand (CD30L), CD40 ligand (CD40L), TNF-related apoptosis-inducing ligand (TRAIL, also designated AGP-1), osteoprotegerin binding protein (OPG-BP or OPG ligand), 4-1BB ligand, LIGHT, APRIL, and TALL-1. Smith et al. (1994), Cell 76: 959-962; Lacey et al. (1998), Cell 93: 165-176; Chichepotiche et al. (1997), J. Biol. Chem. 272: 32401-32410; Mauri et al. (1998), Immunity 8: 21-30; Hahne et al. (1998), J. Exp. Med. 188: 1185-90; Shu et al. (1999), J. Leukocyte Biology 65: 680-3. This family is unified by its structure, particularly at the C-terminus. In addition, most members known to date are expressed in immune compartments, although some members are also expressed in other tissues or organs, as well. Smith et al. (1994), Cell 76: 959-62. All ligand members, with the exception of LT-α, are type II transmembrane proteins, characterized by a conserved 150 amino acid region within C-terminal extracellular domain. Though restricted to only 20-25% identity, the conserved 150 amino acid domain folds into a characteristic β-pleated sheet sandwich and trimerizes. This conserved region can be proteolytically released, thus generating a soluble functional form. Banner et al. (1993), Cell 73: 431-445.

Many members within this ligand family are expressed in lymphoid enriched tissues and play important roles in the immune system development and modulation. Smith et al. (1994). For example, TNFα is mainly synthesized by macrophages and is an important mediator for inflammatory responses and immune defenses. Tracey & Cerami (1994), Ann. Rev. Med. 45: 491-503. Fas-L, predominantly expressed in activated T cell, modulates TCR-mediated apoptosis of thymocytes. Nagata, S. & Suda, T. (1995) Immunology Today 16: 39-43; Castrim et al. (1996), Immunity 5: 617-27. CD40L, also expressed by activated T cells, provides an essential signal for B cell survival, proliferation and immunoglobulin isotype switching. Noelle (1996), Immunity 4: 415-9.

The cognate receptors for most of the TNF ligand family members have been identified. These receptors share characteristic multiple cysteine-rich repeats within their extracellular domains, and do not possess catalytic motifs within cytoplasmic regions. Smith et al. (1994). The receptors signal through direct interactions with death domain proteins (e.g. TRADD, FADD, and RIP) or with the TRAF proteins (e.g. TRAF2, TRAF3, TRAF5, and TRAF6), triggering divergent and overlapping signaling pathways, e.g. apoptosis, NF-κB activation, or JNK activation. Wallach et al. (1999), Annual Review of Immunology 17: 331-67. These signaling events lead to cell death, proliferation, activation or differentiation. The expression profile of each receptor member varies. For example, TNFR1 is expressed on a broad spectrum of tissues and cells, whereas the cell surface receptor of OPGL is mainly restricted to the osteoclasts. Hsu et al. (1999) Proc. Natl. Acad. Sci. USA 96: 3540-5.

A number of research groups have recently identified TNF family ligands with the same or substantially similar sequence. The ligand has been variously named neutrokine α (WO 98/18921, published May 7, 1998), 63954 (WO 98/27114, published June 25, 1998), TL5 (EP 869 180, published October 7, 1998), NTN-2 (WO 98/55620 and WO 98/55621,

published December 10, 1998), TNRL1-alpha (WO 9911791, published March 11, 1999), kay ligand (WO99/12964, published March 18, 1999), and AGP-3 (U.S. Prov. App. Nos. 60/119,906, filed February 12, 1999 and 60/166,271, filed November 18, 1999, respectively); and TALL-1 (WO 00/68378, published Nov. 16, 2000). Each of these references is hereby incorporated by reference. Hereinafter, the ligands reported therein are collectively referred to as TALL-1.

TALL-1 is a member of the TNF ligand superfamily that is functionally involved in B cell survival and proliferation. Transgenic mice overexpressing TALL-1 had severe B cell hyperplasia and lupus-like autoimmune disease. Khare et al. (2000) PNAS 97(7):3370-3375). Both TACI and BCMA serve as cell surface receptors for TALL-1. Gross et al. (2000), Nature **404**: 995-999; Ware (2000), J. Exp. Med. **192**(11): F35-F37; Ware (2000), Nature **404**: 949-950; Xia et al. (2000), J. Exp. Med. **192**(1):137-143; Yu et al. (2000), Nature Immunology **1**(3):252-256; Marsters et al. (2000), Current Biology **10**:785-788; Hatzoglou et al. (2000) J. of Immunology **165**:1322-1330; Shu et al. (2000) PNAS **97**(16):9156-9161; Thompson et al. (2000) J. Exp. Med. **192**(1):129-135; Mukhopadhyay et al. (1999) J. Biol. Chem. **274**(23): 15978-81; Shu et al. (1999) J. Leukocyte Biol. **65**:680-683; Gruss et al. (1995) Blood **85**(12): 3378-3404; Smith et al. (1994), Cell **76**: 959-962; U.S. Pat. No. 5,969,102, issued October 19, 1999; WO 00/67034, published November 9, 2000; WO 00/40716, published July 13, 2000; WO 99/35170, published July 15, 1999. Both receptors are expressed on B cells and signal through interaction with TRAF proteins. In addition, both TACI and BCMA also bind to another TNF ligand family member, APRIL. Yu et al. (2000), Nature Immunology 1(3) :252-256. APRIL has also been demonstrated to induce B cell proliferation.

To date, no recombinant or modified proteins employing peptide modulators of TALL-1 have been disclosed. Recombinant and modified

proteins are an emerging class of therapeutic agents. Useful modifications of protein therapeutic agents include combination with the "Fc" domain of an antibody and linkage to polymers such as polyethylene glycol (PEG) and dextran. Such modifications are discussed in detail in a patent application entitled, "Modified Peptides as Therapeutic Agents," publicshed WO 00/24782, which is hereby incorporated by reference in its entirety.

A much different approach to development of therapeutic agents is peptide library screening. The interaction of a protein ligand with its receptor often takes place at a relatively large interface. However, as demonstrated for human growth hormone and its receptor, only a few key residues at the interface contribute to most of the binding energy. Clackson et al. (1995), Science 267: 383-6. The bulk of the protein ligand merely displays the binding epitopes in the right topology or serves functions unrelated to binding. Thus, molecules of only "peptide" length (2 to 40 amino acids) can bind to the receptor protein of a given large protein ligand. Such peptides may mimic the bioactivity of the large protein ligand ("peptide agonists") or, through competitive binding, inhibit the bioactivity of the large protein ligand ("peptide antagonists").

Phage display peptide libraries have emerged as a powerful method in identifying such peptide agonists and antagonists. See, for example, Scott et al. (1990), Science 249: 386; Devlin et al. (1990), Science 249: 404; U.S. Pat. No. 5,223,409, issued June 29, 1993; U.S. Pat. No. 5,733,731, issued March 31, 1998; U.S. Pat. No. 5,498,530, issued March 12, 1996; U.S. Pat. No. 5,432,018, issued July 11, 1995; U.S. Pat. No. 5,338,665, issued August 16, 1994; U.S. Pat. No. 5,922,545, issued July 13, 1999; WO 96/40987, published December 19, 1996; and WO 98/15833, published April 16, 1998 (each of which is incorporated by reference in its entirety). In such libraries, random peptide sequences are displayed by fusion with

coat proteins of filamentous phage. Typically, the displayed peptides are affinity-eluted against an immobilized target protein. The retained phages may be enriched by successive rounds of affinity purification and repropagation. The best binding peptides may be sequenced to identify key residues within one or more structurally related families of peptides. See, e.g., Cwirla et al. (1997), Science 276: 1696-9, in which two distinct families were identified. The peptide sequences may also suggest which residues may be safely replaced by alanine scanning or by mutagenesis at the DNA level. Mutagenesis libraries may be created and screened to further optimize the sequence of the best binders. Lowman (1997), Ann. Rev. Biophys. Biomol. Struct. 26: 401-24.

Structural analysis of protein-protein interaction may also be used to suggest peptides that mimic the binding activity of large protein ligands. In such an analysis, the crystal structure may suggest the identity and relative orientation of critical residues of the large protein ligand, from which a peptide may be designed. See, e.g., Takasaki et al. (1997), Nature Biotech. 15: 1266-70. These analytical methods may also be used to investigate the interaction between a receptor protein and peptides selected by phage display, which may suggest further modification of the peptides to increase binding affinity.

Other methods compete with phage display in peptide research. A peptide library can be fused to the carboxyl terminus of the lac repressor and expressed in E. coli. Another E. coli-based method allows display on the cell's outer membrane by fusion with a peptidoglycan-associated lipoprotein (PAL). Hereinafter, these and related methods are collectively referred to as "E. coli display." In another method, translation of random RNA is halted prior to ribosome release, resulting in a library of polypeptides with their associated RNA still attached. Hereinafter, this and related methods are collectively referred to as "ribosome display."

Other methods employ peptides linked to RNA; for example, PROfusion technology, Phylos, Inc. See, for example, Roberts & Szostak (1997), Proc. Natl. Acad. Sci. USA, 94: 12297-303. Hereinafter, this and related methods are collectively referred to as "RNA-peptide screening." Chemically derived peptide libraries have been developed in which peptides are immobilized on stable, non-biological materials, such as polyethylene rods or solvent-permeable resins. Another chemically derived peptide library uses photolithography to scan peptides immobilized on glass slides. Hereinafter, these and related methods are collectively referred to as "chemical-peptide screening." Chemical-peptide screening may be advantageous in that it allows use of D-amino acids and other unnatural analogues, as well as non-peptide elements. Both biological and chemical methods are reviewed in Wells & Lowman (1992), Curr. Opin. Biotechnol. 3: 355-62. Conceptually, one may discover peptide mimetics of any protein using phage display, RNA-peptide screening, and the other methods mentioned above.

Summary of the Invention

The present invention concerns therapeutic agents that modulate the activity of TALL-1. In accordance with the present invention, modulators of TALL-1 may comprise an amino acid sequence Dz^2Lz^4 (SEQ ID NO: 108) wherein z^2 is an amino acid residue and z^4 is threonyl or isoleucyl. Such modulators of TALL-1 comprise molecules of the following formulae:

I(a) $a^1a^2a^3CDa^6La^8a^9a^{10}Ca^{12}a^{13}a^{14}$

(SEQ. ID. NO: 100)

wherein:

a^1, a^2, a^3 are each independently absent or amino acid residues;

a^6 is an amino acid residue;

a^9 is a basic or hydrophobic residue;

a^8 is threonyl or isoleucyl;

a^{12} is a neutral polar residue; and

a^{13} and a^{14} are each independently absent or amino acid residues.

I(b) $b^1b^2b^3Cb^5b^6Db^8Lb^{10}b^{11}b^{12}b^{13}b^{14}Cb^{16}b^{17}b^{18}$

(SEQ. ID. NO: 104)

wherein:

b^1 and b^2 are each independently absent or amino acid residues;

b^3 is an acidic or amide residue;

b^5 is an amino acid residue;

b^6 is an aromatic residue;

b^8 is an amino acid residue;

b^{10} is T or I;

b^{11} is a basic residue;

b^{12} and b^{13} are each independently amino acid residues;

b^{14} is a neutral polar residue; and

b^{16}, b^{17}, and b^{18} are each independently absent or amino acid residues.

I(c) $c^1c^2c^3Cc^5Dc^7Lc^9c^{10}c^{11}c^{12}c^{13}c^{14}Cc^{16}c^{17}c^{18}$

(SEQ. ID. NO:105)

wherein:

c^1, c^2, and c^3 are each independently absent or amino acid residues;

c^5 is an amino acid residue;

c^7 is an amino acid residue;

c^9 is T or I;

c^{10} is a basic residue;

c^{11} and c^{12} are each independently amino acid residues;

c^{13} is a neutral polar residue;

c^{14} is an amino acid residue;

c^{16} is an amino acid residue;

c^{17} is a neutral polar residue; and

c^{18} is an amino acid residue or is absent.

I(d) $d^1d^2d^3Cd^5d^6d^7WDd^{10}Ld^{12}d^{13}d^{14}Cd^{15}d^{16}d^{17}$

(SEQ. ID. NO: 106)

wherein:

d^1, d^2, and d^3 are each independently absent or amino acid residues;

d^5, d^6, and d^7 are each independently amino acid residues;

d^{10} is an amino acid residue;

d^{13} is T or I;

d^{14} is an amino acid residue; and

d^{16}, d^{17}, and d^{18} are each independently absent or amino acid residues.

I(e) $e^1e^2e^3Ce^5e^6e^7De^9Le^{11}Ke^{13}Ce^{15}e^{16}e^{17}e^{18}$

(SEQ. ID. NO: 107)

wherein:

e^1, e^2, and e^3 are each independently absent or amino acid residues;

e^5, e^6, e^7, e^9, and e^{13} are each independently amino acid residues;

e^{11} is T or I; and

e^{15}, e^{16}, and e^{17} are each independently absent or amino acid residues.

I(f) $f^1f^2f^3Kf^5Df^7Lf^9f^{10}Qf^{12}f^{13}f^{14}$

(SEQ. ID NO: 109)

wherein:

f^1, f^2, and f^3 are absent or are amino acid residues (with one of f^1, f^2, and f^3 preferred to be C when one of f^{12}, f^{13}, and f^{14} is C);

f^5 is W, Y, or F (W preferred);

f^7 is an amino acid residue (L preferred);

f^9 is T or I (T preferred);

f^{10} is K, R, or H (K preferred);

f^{12} is C, a neutral polar residue, or a basic residue (W, C, or R preferred);

f^{13} is C, a neutral polar residue or is absent (V preferred); and

f^{14} is any amino acid residue or is absent;

provided that only one of f^1, f^2, and f^3 may be C, and only one of f^{12}, f^{13}, and f^{14} may be C.

Compounds of formulae I(a) through I(f) above incorporate Dz^2Lz^4, as well as SEQ ID NO: 63 hereinafter. The sequence of I(f) was derived as a consensus sequence as described in Example 1 hereinbelow. Of compounds within formula I(f), those within the formula

I(f') $f^1f^2f^3KWDf^7Lf^9KQf^{12}f^{13}f^{14}$

(SEQ ID NO: 125)

are preferred. Compounds falling within formula I(f') include SEQ ID NOS: 32, 58, 60, 62, 63, 66, 67, 69, 70, 114, 115, 122, 123, 124, 147-150, 152-177, 179, 180, 187.

Also in accordance with the present invention are compounds having the consensus motif:

PFPWE

(SEQ ID NO: 110)

which also bind TALL-1.

Further in accordance with the present invention are compounds of the formulae:

I(g) $g^1g^2g^3Cg^5PFg^8Wg^{10}Cg^{11}g^{12}g^{13}$

(SEQ. ID. NO. 101)

wherein:

g^1, g^2 and g^3 are each independently absent or amino acid residues;

g^5 is a neutral polar residue;

g^8 is a neutral polar residue;

g^{10} is an acidic residue;

g^{12} and g^{13} are each independently amino acid residues; and

g^{14} is absent or is an amino acid residue.

I(h) $h^1h^2h^3CWh^6h^7WGh^{10}Ch^{12}h^{13}h^{14}$

(SEQ. ID. NO: 102)

wherein:

h^1, h^2, and h^3 are each independently absent or amino acid residues;

h^6 is a hydrophobic residue;

h^7 is a hydrophobic residue;

h^{10} is an acidic or polar hydrophobic residue; and

h^{12}, h^{13}, and h^{14} are each independently absent or amino acid residues.

I(i) $i^1i^2i^3Ci^5i^6i^7i^8i^9i^{10}Ci^{12}i^{13}i^{14}$

(SEQ. ID. NO: 103)

wherein:

i^1 is absent or is an amino acid residue;

i^2 is a neutral polar residue;

i^3 is an amino acid residue;

i^5, i^6, i^7, and i^8 are each independently amino acid residues;

i^9 is an acidic residue;

i^{10} is an amino acid residue;

i^{12} and i^{13} are each independently amino acid residues; and

i^{14} is a neutral polar residue.

The compounds defined by formulae I(g) through I(i) also bind TALL-1.

Further in accordance with the present invention, modulators of TALL-1 comprise:

a) a TALL-1 modulating domain (e.g., an amino acid sequence of Formulae I(a) through I(i)), preferably the amino acid sequence Dz^2Lz^4, or sequences derived therefrom by phage display, RNA-peptide screening, or the other techniques mentioned above; and

b) a vehicle, such as a polymer (e.g., PEG or dextran) or an Fc domain, which is preferred;

wherein the vehicle is covalently attached to the TALL-1 modulating domain. The vehicle and the TALL-1 modulating domain may be linked through the N- or C-terminus of the TALL-1 modulating domain, as described further below. The preferred vehicle is an Fc domain, and the preferred Fc domain is an IgG Fc domain. Such Fc-linked peptides are referred to herein as "peptibodies." Preferred TALL-1 modulating domains comprise the amino acid sequences described hereinafter in Tables 1 and 2. Other TALL-1 modulating domains can be generated by phage display, RNA-peptide screening and the other techniques mentioned herein.

Further in accordance with the present invention is a process for making TALL-1 modulators, which comprises:

a. selecting at least one peptide that binds to TALL-1 ; and

b. covalently linking said peptide to a vehicle.

The preferred vehicle is an Fc domain. Step (a) is preferably carried out by selection from the peptide sequences in Table 2 hereinafter or from phage display, RNA-peptide screening, or the other techniques mentioned herein.

The compounds of this invention may be prepared by standard synthetic methods, recombinant DNA techniques, or any other methods of preparing peptides and fusion proteins. Compounds of this invention that encompass non-peptide portions may be synthesized by standard organic chemistry reactions, in addition to standard peptide chemistry reactions when applicable.

The primary use contemplated for the compounds of this invention is as therapeutic or prophylactic agents. The vehicle-linked peptide may

have activity comparable to—or even greater than—the natural ligand mimicked by the peptide.

The compounds of this invention may be used for therapeutic or prophylactic purposes by formulating them with appropriate pharmaceutical carrier materials and administering an effective amount to a patient, such as a human (or other mammal) in need thereof. Other related aspects are also included in the instant invention.

Numerous additional aspects and advantages of the present invention will become apparent upon consideration of the figures and detailed description of the invention.

Brief Description of the Figures

Figure 1 shows exemplary Fc dimers that may be derived from an IgG1 antibody. "Fc" in the figure represents any of the Fc variants within the meaning of "Fc domain" herein. "X^1" and "X^2" represent peptides or linker-peptide combinations as defined hereinafter. The specific dimers are as follows:

A, D: Single disulfide-bonded dimers. IgG1 antibodies typically have two disulfide bonds at the hinge region of the antibody. The Fc domain in Figures 1A and 1 D may be formed by truncation between the two disulfide bond sites or by substitution of a cysteinyl residue with an unreactive residue (e.g., alanyl). In Figure 1A, the Fc domain is linked at the amino terminus of the peptides; in 1D, at the carboxyl terminus.

B, E: Doubly disulfide-bonded dimers. This Fc domain may be formed by truncation of the parent antibody to retain both cysteinyl residues in the Fc domain chains or by expression from a construct including a sequence encoding such an Fc domain. In Figure 1B, the Fc domain is linked at the amino terminus of the peptides; in 1E, at the carboxyl terminus.

C, F: Noncovalent dimers. This Fc domain may be formed by elimination of the cysteinyl residues by either truncation or substitution. One may desire to eliminate the cysteinyl residues to avoid impurities formed by reaction of the cysteinyl residue with cysteinyl residues of other proteins present in the host cell. The noncovalent bonding of the Fc domains is sufficient to hold together the dimer.
Other dimers may be formed by using Fc domains derived from different types of antibodies (e.g., IgG2, IgM).

Figure 2 shows the structure of preferred compounds of the invention that feature tandem repeats of the pharmacologically active peptide. Figure 2A shows a single chain molecule and may also represent the DNA construct for the molecule. Figure 2B shows a dimer in which the linker-peptide portion is present on only one chain of the dimer. Figure 2C shows a dimer having the peptide portion on both chains. The dimer of Figure 2C will form spontaneously in certain host cells upon expression of a DNA construct encoding the single chain shown in Figure 3A. In other host cells, the cells could be placed in conditions favoring formation of dimers or the dimers can be formed in vitro.

Figure 3 shows exemplary nucleic acid and amino acid sequences (SEQ ID NOS: 1 and 2, respectively) of human IgG1 Fc that may be used in this invention.

Figures 4A through 4F show the nucleotide and amino acid sequences (SEQ ID NOS: 3-27) S of NdeI to SalI fragments encoding peptide and linker.

Figures 5A through 5M show the nucleotide sequence (SEQ ID NO: 28) of pAMG21-RANK-Fc vector, which was used to construct Fc-linked molecules of the present invention. These figures identify a number of features of the nucleic acid, including:

- promoter regions PcopB, PrepA, RNAI, APHII, luxPR, and luxPL;
- mRNA for APHII, luxR;

- coding sequences and amino acid sequences for the proteins copB protein, copT, repAI, repA4, APHII, luxR, RANK, and Fc;
- binding sites for the proteins copB, CRP;
- hairpins T1, T2, T7, and toop;
- operator site for lux protein;
- enzyme restriction sites for PflII08I, BglII, ScaI, BmnI, DrdII, DraIII, BstBI, AceIII, AflII, PflMI, BglI, SfiI, BstEII, BspLulII, NspV, BplI, EagI, BcgI, NsiI, BsaI, Pspl406I, AatII, BsmI, NruI, NdeI, ApaLI, Acc65I, KpnI, SalI, AccI, BspEI, AhdI, BspHI, EconI, BsrGI, BmaI, SmaI, SexAI, BamHI, and BlpI.

Figures 6A and 6B show the DNA sequence (SEQ ID NO: 97) inserted into pCFM1656 between the unique AatII (position #4364 in pCFM1656) and SacII (position #4585 in pCFM1656) restriction sites to form expression plasmid pAMG21 (ATCC accession no. 98113).

Figure 7 shows that the TALL-1 peptibody (SEQ ID NO: 70) inhibits TALL-1-mediated B cell proliferation. Purified B cells (10^5) from B6 mice were cultured in triplicates in 96-well plated with the indicated amounts of TALL-1 consensus peptibody in the presence of 10 ng/ml TALL-1 plus 2 μg/ml anti-IgM antibody. Proliferation was measured by radioactive [^{3}H]thymidine uptake in the last 18h of pulse. Data shown represent mean ± SD triplicate wells.

Figure 8 shows that a TALL-1 N-terminal tandem dimer peptibodies (SEQ ID NO: 123, 124 in Table 5B hereinafter) are preferable for inhibition of TALL-1-mediated B cell proliferation. Purified B cells (10^5) from B6 mice were cultured in triplicates in 96-well plated with the indicated amounts of TALL-1 12-3 peptibody and TALL-1 consensus peptibody (SEQ ID NOS: 115 and 122 of Table 5B)or the related dimer peptibodies (SEQ ID NOS: 123, 124) in the presence of 10 ng/ml TALL-1 plus 2 μg/ml anti-IgM antibody. Proliferation was measured by radioactive [^{3}H]thymidine uptake in the last 18h of pulse. Data shown represent mean ± SD triplicate wells.

Figure 9. AGP3 peptibody binds to AGP3 with high affinity. Dissociation equilibrium constant (K_D) was obtained from nonlinear regression

of the competition curves using a dual-curve one-site homogeneous binding model (KinEx™ software). K_D is about 4 pM for AGP3 peptibody binding with human AGP3 (SEQ ID NO: 123).

Figures 10A and 10B. AGP3 peptibody blocks both human and murine AGP3 in the Biacore competition assay. Soluble human TACI protein was immobilized to B1 chip. 1 nM of recombinant human AGP3 protein (upper panel) or 5 nM of recombinant murine AGP3 protein (lower panel) was incubated with indicated amount of AGP3 peptibody before injected over the surface of receptor. Relative human AGP3 and murine AGP3 (binding response was shown (SEQ ID NO: 123).

Figures 11A and 11B. AGP3 peptibody blocked AGP3 binding to all three receptors TACI, BCMA and BAFFR in Biacore competition assay. Recombinant soluble receptor TACI, BCMA and BAFFR proteins were immobilized to CM5 chip. 1 nM of recombinant human AGP3 (upper panel) were incubated with indicated amount of AGP3 peptibody before injected over each receptor surface. Relative binding of AGP3 was measured. Similarly, 1 nM of recombinant APRIL protein was incubated with indicated amount of AGP3 peptibody before injected over each receptor surface. AGP3 peptibody didn't inhibit APRIL binding to all three receptors (SEQ ID NO: 123).

Figures 12A and 12B. AGP3 peptibody inhibits mouse serum immunoglobulin level increase induced by human AGP3 challenge. Balb/c mice received 7 daily intraperitoneal injections of 1 mg/Kg human AGP3 protein along with saline, human Fc, or AGP3 peptibody at indicated doses, and were bled on day 8. Serum total IgM and IgA level were measured by ELISA (SEQ ID NO: 123).

Figure 13. AGP3 peptibody treatment reduced arthritis severity in the mouse CIA model. Eight to 12 weeks old DBA/1 male mice were immunized with bovine collagen type II (bCII) emulsified in complete freunds adjuvant intradermally at the base of tail, and were boosted 3 weeks after the initial immunization with bCII emulsified in incomplete freunds adjuvant. Treatment with indicated dosage of AGP3 peptibody was begun from the day of booster

immunization for 4 weeks. As described before (Khare et al., *J. Immunol.*. 155: 3653-9, 1995), all four paws were individually scored from 0-3 for arthritis severity (SEQ ID NO: 123).

Figure 14. AGP3 peptibody treatment inhibited anti-collagen antibody generation in the mouse CIA model. Serum samples were taken one week after final treatment (day 35) as described above. Serum anti-collagen II antibody level was determined by ELISA analysis (SEQ ID NO: 123).

Figures 15A and 15B. AGP3 peptibody treatment delayed proteinuria onset and improved survival in NZB/NZW lupus mice. Five-month-old lupus prone NZBx NZBWF1 mice were treated i.p. 3X/week for 8 weeks with PBS or indicated doses of AGP3 peptibody (SEQ ID NO: 123) or human Fc proteins. Protein in the urine was evaluated monthly throughout the life of the experiment with Albustix reagent strips (Bayer AG).

Figures 16A and 16B show the nucleic acid and amino acid sequences of a preferred TALL-1-binding peptibody (SEQ ID NOS: 189 and 123)

Detailed Description of the Invention

Definition of Terms

The terms used throughout this specification are defined as follows, unless otherwise limited in specific instances.

General definitions

The term "comprising" means that a compound may include additional amino acids on either or both of the N- or C- termini of the given sequence. Of course, these additional amino acids should not significantly interfere with the activity of the compound.

Additionally, physiologically acceptable salts of the compounds of this invention are also encompassed herein. The term "physiologically acceptable salts" refers to any salts that are known or later discovered to be pharmaceutically acceptable. Some specific examples are: acetate;

trifluoroacetate; hydrohalides, such as hydrochloride and hydrobromide; sulfate; citrate; tartrate; glycolate; and oxalate.

Amino acids

The term "acidic residue" refers to amino acid residues in D- or L-form having sidechains comprising acidic groups. Exemplary acidic residues include D and E.

The term "amide residue" refers to amino acids in D- or L-form having sidechains comprising amide derivatives of acidic groups. Exemplary residues include N and Q.

The term "aromatic residue" refers to amino acid residues in D- or L-form having sidechains comprising aromatic groups. Exemplary aromatic residues include F, Y, and W.

The term "basic residue" refers to amino acid residues in D- or L-form having sidechains comprising basic groups. Exemplary basic residues include H, K, and R.

The term "hydrophilic residue" refers to amino acid residues in D- or L-form having sidechains comprising polar groups. Exemplary hydrophilic residues include C, S, T, N, and Q.

The term "nonfunctional residue" refers to amino acid residues in D- or L-form having sidechains that lack acidic, basic, or aromatic groups. Exemplary nonfunctional amino acid residues include M, G, A, V, I, L and norleucine (Nle).

The term "neutral polar residue" refers to amino acid residues in D- or L-form having sidechains that lack basic, acidic, or polar groups. Exemplary neutral polar amino acid residues include A, V, L, I, P, W, M, and F.

The term "polar hydrophobic residue" refers to amino acid residues in D- or L-form having sidechains comprising polar groups. Exemplary polar hydrophobic amino acid residues include T, G, S, Y, C, Q, and N.

The term "hydrophobic residue" refers to amino acid residues in D- or L-form having sidechains that lack basic or acidic groups. Exemplary hydrophobic amino acid residues include A, V, L, I, P, W, M, F, T, G, S, Y, C, Q, and N.

Peptides

The term "peptide" refers to molecules of 1 to 40 amino acids, with molecules of 5 to 20amino acids preferred. Exemplary peptides may comprise the TALL-1 modulating domain of a naturally occurring molecule or comprise randomized sequences.

The term "randomized" as used to refer to peptide sequences refers to fully random sequences (e.g., selected by phage display methods or RNA-peptide screening) and sequences in which one or more residues of a naturally occurring molecule is replaced by an amino acid residue not appearing in that position in the naturally occurring molecule. Exemplary methods for identifying peptide sequences include phage display, E. coli display, ribosome display, RNA-peptide screening, chemical screening, and the like.

The term " TALL-1 modulating domain" refers to any amino acid sequence that binds to the TALL-1 and comprises naturally occurring sequences or randomized sequences. Exemplary TALL-1 modulating domains can be identified or derived by phage display or other methods mentioned herein.

The term " TALL-1 antagonist" refers to a molecule that binds to the TALL-1 and increases or decreases one or more assay parameters opposite from the effect on those parameters by full length native TALL-1. Such activity can be determined, for example, by such assays as described in the subsection entitled "Biological activity of AGP-3" in the Materials & Methods section of the patent application entitled, "TNF-RELATED PROTEINS", WO 00/47740, published August 17, 2000.

Vehicles and peptibodies

The term "vehicle" refers to a molecule that prevents degradation and/or increases half-life, reduces toxicity, reduces immunogenicity, or increases biological activity of a therapeutic protein. Exemplary vehicles include an Fc domain (which is preferred) as well as a linear polymer (e.g., polyethylene glycol (PEG), polylysine, dextran, etc.); a branched-chain polymer (see, for example, U.S. Patent No. 4,289,872 to Denkenwalter et al., issued September 15, 1981; 5,229,490 to Tam, issued July 20, 1993; WO 93/21259 by Frechet et al., published 28 October 1993); a lipid; a cholesterol group (such as a steroid); a carbohydrate or oligosaccharide (e.g., dextran); any natural or synthetic protein, polypeptide or peptide that binds to a salvage receptor; albumin, including human serum albumin (HSA), leucine zipper domain, and other such proteins and protein fragments. Vehicles are further described hereinafter.

The term "native Fc" refers to molecule or sequence comprising the sequence of a non-antigen-binding fragment resulting from digestion of whole antibody, whether in monomeric or multimeric form. The original immunoglobulin source of the native Fc is preferably of human origin and may be any of the immunoglobulins, although IgG1 and IgG2 are preferred. Native Fc's are made up of monomeric polypeptides that may be linked into dimeric or multimeric forms by covalent (i.e., disulfide bonds) and non-covalent association. The number of intermolecular disulfide bonds between monomeric subunits of native Fc molecules ranges from 1 to 4 depending on class (e.g., IgG, IgA, IgE) or subclass (e.g., IgG1, IgG2, IgG3, IgA1, IgGA2). One example of a native Fc is a disulfide-bonded dimer resulting from papain digestion of an IgG (see Ellison et al.

(1982), Nucleic Acids Res. 10: 4071-9). The term "native Fc" as used herein is generic to the monomeric, dimeric, and multimeric forms.

The term "Fc variant" refers to a molecule or sequence that is modified from a native Fc but still comprises a binding site for the salvage receptor, FcRn. International applications WO 97/34631 (published 25 September 1997) and WO 96/32478 describe exemplary Fc variants, as well as interaction with the salvage receptor, and are hereby incorporated by reference in their entirety. Thus, the term "Fc variant" comprises a molecule or sequence that is humanized from a non-human native Fc. Furthermore, a native Fc comprises sites that may be removed because they provide structural features or biological activity that are not required for the fusion molecules of the present invention. Thus, the term "Fc variant" comprises a molecule or sequence that lacks one or more native Fc sites or residues that affect or are involved in (1) disulfide bond formation, (2) incompatibility with a selected host cell (3) N-terminal heterogeneity upon expression in a selected host cell, (4) glycosylation, (5) interaction with complement, (6) binding to an Fc receptor other than a salvage receptor, or (7) antibody-dependent cellular cytotoxicity (ADCC). Fc variants are described in further detail hereinafter.

The term "Fc domain" encompasses native Fc and Fc variant molecules and sequences as defined above. As with Fc variants and native Fc's, the term "Fc domain" includes molecules in monomeric or multimeric form, whether digested from whole antibody or produced by other means.

The term "multimer" as applied to Fc domains or molecules comprising Fc domains refers to molecules having two or more polypeptide chains associated covalently, noncovalently, or by both covalent and non-covalent interactions. IgG molecules typically form dimers; IgM, pentamers; IgD, dimers; and IgA, monomers, dimers,

trimers, or tetramers. Multimers may be formed by exploiting the sequence and resulting activity of the native Ig source of the Fc or by derivatizing (as defined below) such a native Fc.

The term "dimer" as applied to Fc domains or molecules comprising Fc domains refers to molecules having two polypeptide chains associated covalently or non-covalently. Thus, exemplary dimers within the scope of this invention are as shown in Figure 1.

The terms "derivatizing" and "derivative" or "derivatized" comprise processes and resulting compounds respectively in which (1) the compound has a cyclic portion; for example, cross-linking between cysteinyl residues within the compound; (2) the compound is cross-linked or has a cross-linking site; for example, the compound has a cysteinyl residue and thus forms cross-linked dimers in culture or in vivo; (3) one or more peptidyl linkage is replaced by a non-peptidyl linkage; (4) the N-terminus is replaced by -NRR^1, NRC(O)R^1, -NRC(O)OR^1, -NRS(O)$_2$R^1, -NHC(O)NHR, a succinimide group, or substituted or unsubstituted benzyloxycarbonyl-NH-, wherein R and R^1 and the ring substituents are as defined hereinafter; (5) the C-terminus is replaced by -C(O)R^2 or -NR^{3}R^4 wherein R^2, R^3 and R^4 are as defined hereinafter; and (6) compounds in which individual amino acid moieties are modified through treatment with agents capable of reacting with selected side chains or terminal residues. Derivatives are further described hereinafter.

The terms "peptibody" and "peptibodies" refer to molecules comprising an Fc domain and at least one peptide. Such peptibodies may be multimers or dimers or fragments thereof, and they may be derivatized. In the present invention, the molecules of formulae II through VI hereinafter are peptibodies when V^1 is an Fc domain.

Structure of compounds

In General. The present inventors identified sequences capable of binding to and modulating the biological activity of TALL-1. These sequences can be modified through the techniques mentioned above by which one or more amino acids may be changed while maintaining or even improving the binding affinity of the peptide.

In the compositions of matter prepared in accordance with this invention, the peptide(s) may be attached to the vehicle through the peptide's N-terminus or C-terminus. Any of these peptides may be linked in tandem (i.e., sequentially), with or without linkers. Thus, the vehicle-peptide molecules of this invention may be described by the following formula:

II

$$(X^1)_a\text{-}V^1\text{-}(X^2)_b$$

wherein:

V^1 is a vehicle (preferably an Fc domain);

X^1 and X^2 are each independently selected from $-(L^1)_c\text{-}P^1$, $-(L^1)_c\text{-}P^1\text{-}(L^2)_d\text{-}P^2$, $-(L^1)_c\text{-}P^1\text{-}(L^2)_d\text{-}P^2\text{-}(L^3)_e\text{-}P^3$, and $-(L^1)_c\text{-}P^1\text{-}(L^2)_d\text{-}P^2\text{-}(L^3)_e\text{-}P^3\text{-}(L^4)_f\text{-}P^4$

P^1, P^2, P^3, and P^4 are each independently sequences of TALL-1 modulating domains, such as those of Formulae I(a) through I(i);

L^1, L^2, L^3, and L^4 are each independently linkers; and

a, b, c, d, e, and f are each independently 0 or 1, provided that at least one of a and b is 1.

Thus, compound II comprises preferred compounds of the formulae

III

$$X^1\text{-}V^1$$

and multimers thereof wherein V^1 is an Fc domain and is attached at the C-terminus of A^1;

IV

$$V^1\text{-}X^2$$

and multimers thereof wherein V^1 is an Fc domain and is attached at the N-terminus of A^2;

V

$$V^1\text{-}(L^1)_c\text{-}P^1$$

and multimers thereof wherein V^1 is an Fc domain and is attached at the N-terminus of $\text{-}(L^1)_c\text{-}P^1$; and

VI

$$V^1\text{-}(L^1)_c\text{-}P^1\text{-}(L^2)_d\text{-}P^2$$

and multimers thereof wherein V^1 is an Fc domain and is attached at the N-terminus of $\text{-}L^1\text{-}P^1\text{-}L^2\text{-}P^2$.

Peptides. The peptides of this invention are useful as TALL-1 modulating peptides or as TALL-1 modulating domains in the molecules of formulae II through VI. Molecules of this invention comprising these peptide sequences may be prepared by methods known in the art.

Preferred peptide sequences are those of the foregoing formulae I(a) having the substituents identified below.

Table 1--Preferred peptide substituents

Formula I(a)	a^8 is T; a^9 is a basic residue (K most preferred); and a^{12} is a neutral polar residue (F most preferred).
Formula I(b)	b^3 is D, Q, or E; b^6 is W or Y; b^{10} is T; b^{11} is K or R; and b^{14} is V or L.
Formula I(c)	c^9 is T ; c^{10} is K or R; c^{13} is a I, L, or V; and c^{17} is A or L.
Formula I(d)	d^{13} is T.
Formula I(e)	e^{11} is T.
Formula I(f)	f^6 is T; f^7 is K; and f^{10} is V.
Formula I(g)	g^5 is W; g^8 is P; g^{10} is E; and g^{13} is a basic residue.
Formula I(h)	h^1 is G; h^6 is A; h^7 is a neutral polar residue; and h^{10} is an acidic residue.
Formula I(i)	i^2 is W; and i^{14} is W.

Preferred peptide sequences appear in Table 2 below.

Table 2—Preferred TALL-1 modulating domains

Sequence	SEQ ID NO:
PGTCFPFPWECTHA	29
WGACWPFPWECFKE	30
VPFCDLLTKHCFEA	31
GSRCKYKWDVLTKQCFHH	32
LPGCKWDLLIKQWVCDPL	33
SADCYFDILTKSDVCTSS	34
SDDCMYDQLTRMFICSNL	35
DLNCKYDELTYKEWCQFN	36
FHDCKYDLLTRQMVCHGL	37
RNHCFWDHLLKQDICPSP	38
ANQCWWDSLTKKNVCEFF	39
YKGRQMWDILTRSWVVSL	126
QDVGLWWDILTRAWMPNI	127
QNAQRVWDLLIRTWVYPQ	128
GWNEAWWDELTKIWVLEQ	129
RITCDTWDSLIKKCVPQS	130
GAIMQFWDSLTKTWLRQS	131
WLHSGWWDPLTKHWLQKV	132
SEWFFWFDPLTRAQLKFR	133
GVWFWWFDPLTKQWTQAG	134
MQCKGYYDILTKWCVTNG	135
LWSKEVWDILTKSWVSQA	136
KAAGWWFDWLTKVWVPAP	137
AYQTWFWDSLTRLWLSTT	138
SGQHFWWDLLTRSWTPST	139
LGVGQKWDPLTKQWVSRG	140
VGKMCQWDPLIKRTVCVG	141
CRQGAKFDLLTKQCLLGR	142
GQAIRHWDVLTKQWVDSQ	143
RGPCGSWDLLTKHCLDSQ	144
WQWKQQWDLLTKQMVWVG	145
PITICRKDLLTKQVVCLD	146
KTCNGKWDLLTKQCLQQA	147
KCLKGKWDLLTKQCVTEV	148
RCWNGKWDLLTKQCIHPW	149
NRDMRKWDPLIKQWIVRP	150
QAAAATWDLLTKQWLVPP	151
PEGGPKWDPLTKQFLPPV	152
QTPQKKWDLLTKQWFTRN	153
IGSPCKWDLLTKQMICQT	154
CTAAGKWDLLTKQCIQEK	155
VSQCMKWDLLTKQCLQGW	156
VWGTWKWDLLTKQYLPPQ	157
GWWEMKWDLLTKQWYRPQ	158
TAQVSKWDLLTKQWLPLA	159
QLWGTKWDLLTKQYIQIM	160
WATSQKWDLLTKQWVQNM	161
QRQCAKWDLLTKQCVLFY	162

KTTDCKWDLLTKQRICQV	163
LLCQGKWDLLTKQCLKLR	164
LMWFWKWDLLTKQLVPTF	165
QTWAWKWDLLTKQWIGPM	166
NKELLKWDLLTKQCRGRS	167
GQKDLKWDLLTKQYVRQS	168
PKPCQKWDLLTKQCLGSV	169
GQIGWKWDLLTKQWIQTR	170
VWLDWKWDLLTKQWIHPQ	171
QEWEYKWDLLTKQWGWLR	172
HWDSWKWDLLTKQWVVQA	173
TRPLQKWDLLTKQWLRVG	174
SDQWQKWDLLTKQWFWDV	175
QQTFMKWDLLTKQWIRRH	176
QGECRKWDLLTKQCFPGQ	177
GQMGWRWDPLIKMCLGPS	178
QLDGCKWDLLTKQKVCIP	179
HGYWQKWDLLTKQWVSSE	180
HQGQCGWDLLTRIYLPCH	181
LHKACKWDLLTKQCWPMQ	182
GPPGSVWDLLTKIWIQTG	183
ITQDWRFDTLTRLWLPLR	184
QGGFAAWDVLTKMWITVP	185
GHGTPWWDALTRIWILGV	186
VWPWQKWDLLTKQFVFQD	187
WQWSWKWDLLTRQYISSS	188
NQTLWKWDLLTKQFITYM	60
PVYQGWWDTLTKLYIWDG	61
WLDGGWRDPLIKRSVQLG	62
GHQQFKWDLLTKQWVQSN	63
QRVGQFWDVLTKMFITGS	64
QAQGWSYDALIKTWIRWP	65
GWMHWKWDPLTKQALPWM	66
GHPTYKWDLLTKQWILQM	67
WNNWSLWDPLTKLWLQQN	68
WQWGWKWDLLTKQWVQQQ	69
GQMGWRWDPLTKMWLGTS	70

It is noted that the known receptors for TALL-1 bear some sequence homology with preferred peptides:

12-3 LPGCKWDLLIKQWVCDPL

BAFFR MRRGPRSLRGRDAPVPTPCVPTECYDLLVRKCVDCRLL

TACI TICNHQSQRTCAAFCRSLSCRKEQGKFYDHLLRDCISCASI

BCMA FVSPSQEIRGRFRRMLQMAGQCSQNEYFDSLLHACIPCQLRC

(SEQ ID NOS: 33, 195, 196, and 197, respectively).

Any peptide containing a cysteinyl residue may be cross-linked with another Cys-containing peptide, either or both of which may be linked to a

vehicle. Any peptide having more than one Cys residue may form an intrapeptide disulfide bond, as well. Any of these peptides may be derivatized as described hereinafter.

Additional useful peptide sequences may result from conservative and/or non-conservative modifications of the amino acid sequences of the sequences in Table 2.

Conservative modifications will produce peptides having functional and chemical characteristics similar to those of the peptide from which such modifications are made. In contrast, substantial modifications in the functional and/or chemical characteristics of the peptides may be accomplished by selecting substitutions in the amino acid sequence that differ significantly in their effect on maintaining (a) the structure of the molecular backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the size of the molecule.

For example, a "conservative amino acid substitution" may involve a substitution of a native amino acid residue with a nonnative residue such that there is little or no effect on the polarity or charge of the amino acid residue at that position. Furthermore, any native residue in the polypeptide may also be substituted with alanine, as has been previously described for "alanine scanning mutagenesis" (see, for example, MacLennan et al., 1998, Acta Physiol. Scand. Suppl. 643:55-67; Sasaki et al., 1998, Adv. Biophys. 35:1-24, which discuss alanine scanning mutagenesis).

Desired amino acid substitutions (whether conservative or non-conservative) can be determined by those skilled in the art at the time such substitutions are desired. For example, amino acid substitutions can be used to identify important residues of the peptide sequence, or to increase or decrease the affinity of the peptide or vehicle-peptide molecules (see preceding formulae) described herein. Exemplary amino acid substitutions are set forth in Table 3.

Table 3—Amino Acid Substitutions

Original Residues	Exemplary Substitutions	Preferred Substitutions
Ala (A)	Val, Leu, Ile	Val
Arg (R)	Lys, Gln, Asn	Lys
Asn (N)	Gln	Gln
Asp (D)	Glu	Glu
Cys (C)	Ser, Ala	Ser
Gln (Q)	Asn	Asn
Glu (E)	Asp	Asp
Gly (G)	Pro, Ala	Ala
His (H)	Asn, Gln, Lys, Arg	Arg
Ile (I)	Leu, Val, Met, Ala, Phe, Norleucine	Leu
Leu (L)	Norleucine, Ile, Val, Met, Ala, Phe	Ile
Lys (K)	Arg, 1,4 Diamino-butyric Acid, Gln, Asn	Arg
Met (M)	Leu, Phe, Ile	Leu
Phe (F)	Leu, Val, Ile, Ala, Tyr	Leu
Pro (P)	Ala	Gly
Ser (S)	Thr, Ala, Cys	Thr
Thr (T)	Ser	Ser
Trp (W)	Tyr, Phe	Tyr
Tyr (Y)	Trp, Phe, Thr, Ser	Phe
Val (V)	Ile, Met, Leu, Phe, Ala, Norleucine	Leu

In certain embodiments, conservative amino acid substitutions also encompass non-naturally occurring amino acid residues which are

typically incorporated by chemical peptide synthesis rather than by synthesis in biological systems.

As noted in the foregoing section "Definition of Terms," naturally occurring residues may be divided into classes based on common sidechain properties that may be useful for modifications of sequence. For example, non-conservative substitutions may involve the exchange of a member of one of these classes for a member from another class. Such substituted residues may be introduced into regions of the peptide that are homologous with non-human orthologs, or into the non-homologous regions of the molecule. In addition, one may also make modifications using P or G for the purpose of influencing chain orientation.

In making such modifications, the hydropathic index of amino acids may be considered. Each amino acid has been assigned a hydropathic index on the basis of their hydrophobicity and charge characteristics, these are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5); glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

The importance of the hydropathic amino acid index in conferring interactive biological function on a protein is understood in the art. Kyte et al., J. Mol. Biol., 157: 105-131 (1982). It is known that certain amino acids may be substituted for other amino acids having a similar hydropathic index or score and still retain a similar biological activity. In making changes based upon the hydropathic index, the substitution of amino acids whose hydropathic indices are within ±2 is preferred, those which are within ±1 are particularly preferred, and those within ±0.5 are even more particularly preferred.

It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. The greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with its immunogenicity and antigenicity, i.e., with a biological property of the protein.

The following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 ± 1); glutamate (+3.0 ± 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (-0.4); proline (-0.5 ± 1); alanine (-0.5); histidine (-0.5); cysteine (-1.0); methionine (-1.3); valine (-1.5); leucine (-1.8); isoleucine (-1.8); tyrosine (-2.3); phenylalanine (-2.5); tryptophan (-3.4). In making changes based upon similar hydrophilicity values, the substitution of amino acids whose hydrophilicity values are within ±2 is preferred, those which are within ±1 are particularly preferred, and those within ±0.5 are even more particularly preferred. One may also identify epitopes from primary amino acid sequences on the basis of hydrophilicity. These regions are also referred to as "epitopic core regions."

A skilled artisan will be able to determine suitable variants of the polypeptide as set forth in the foregoing sequences using well known techniques. For identifying suitable areas of the molecule that may be changed without destroying activity, one skilled in the art may target areas not believed to be important for activity. For example, when similar polypeptides with similar activities from the same species or from other species are known, one skilled in the art may compare the amino acid sequence of a peptide to similar peptides. With such a comparison, one can identify residues and portions of the molecules that are conserved among similar polypeptides. It will be appreciated that changes in areas of a peptide that are not conserved relative to such similar peptides would

be less likely to adversely affect the biological activity and/or structure of the peptide. One skilled in the art would also know that, even in relatively conserved regions, one may substitute chemically similar amino acids for the naturally occurring residues while retaining activity (conservative amino acid residue substitutions). Therefore, even areas that may be important for biological activity or for structure may be subject to conservative amino acid substitutions without destroying the biological activity or without adversely affecting the peptide structure.

Additionally, one skilled in the art can review structure-function studies identifying residues in similar peptides that are important for activity or structure. In view of such a comparison, one can predict the importance of amino acid residues in a peptide that correspond to amino acid residues that are important for activity or structure in similar peptides. One skilled in the art may opt for chemically similar amino acid substitutions for such predicted important amino acid residues of the peptides.

One skilled in the art can also analyze the three-dimensional structure and amino acid sequence in relation to that structure in similar polypeptides. In view of that information, one skilled in the art may predict the alignment of amino acid residues of a peptide with respect to its three dimensional structure. One skilled in the art may choose not to make radical changes to amino acid residues predicted to be on the surface of the protein, since such residues may be involved in important interactions with other molecules. Moreover, one skilled in the art may generate test variants containing a single amino acid substitution at each desired amino acid residue. The variants can then be screened using activity assays know to those skilled in the art. Such data could be used to gather information about suitable variants. For example, if one discovered that a change to a particular amino acid residue resulted in destroyed,

undesirably reduced, or unsuitable activity, variants with such a change would be avoided. In other words, based on information gathered from such routine experiments, one skilled in the art can readily determine the amino acids where further substitutions should be avoided either alone or in combination with other mutations.

A number of scientific publications have been devoted to the prediction of secondary structure. See Moult J., Curr. Op. in Biotech., 7(4): 422-427 (1996), Chou et al., Biochemistry, 13(2): 222-245 (1974); Chou et al., Biochemistry, 113(2): 211-222 (1974); Chou et al., Adv. Enzymol. Relat. Areas Mol. Biol., 47: 45-148 (1978); Chou et al., Ann. Rev. Biochem., 47: 251-276 and Chou et al., Biophys. J., 26: 367-384 (1979). Moreover, computer programs are currently available to assist with predicting secondary structure. One method of predicting secondary structure is based upon homology modeling. For example, two polypeptides or proteins which have a sequence identity of greater than 30%, or similarity greater than 40% often have similar structural topologies. The recent growth of the protein structural data base (PDB) has provided enhanced predictability of secondary structure, including the potential number of folds within a polypeptide's or protein's structure. See Holm et al., Nucl. Acid. Res., 27(1): 244-247 (1999). It has been suggested (Brenner et al., Curr. Op. Struct. Biol., 7(3): 369-376 (1997)) that there are a limited number of folds in a given polypeptide or protein and that once a critical number of structures have been resolved, structural prediction will gain dramatically in accuracy.

Additional methods of predicting secondary structure include "threading" (Jones, D., Curr. Opin. Struct. Biol., 7(3): 377-87 (1997); Sippl et al., Structure, 4(1): 15-9 (1996)), "profile analysis" (Bowie et al., Science, 253: 164-170 (1991); Gribskov et al., Meth. Enzym., 183: 146-159 (1990);

Gribskov et al., Proc. Nat. Acad. Sci., 84(13): 4355-8 (1987)), and "evolutionary linkage" (See Home, supra, and Brenner, supra).

Vehicles. This invention requires the presence of at least one vehicle (V^1) attached to a peptide through the N-terminus, C-terminus or a sidechain of one of the amino acid residues. Multiple vehicles may also be used; e.g., Fc's at each terminus or an Fc at a terminus and a PEG group at the other terminus or a sidechain. Exemplary vehicles include:

- an Fc domain;
- other proteins, polypeptides, or peptides capable of binding to a salvage receptor;
- human serum albumin (HSA);
- a leucine zipper (LZ) domain;
- polyethylene glycol (PEG), including 5 kD, 20 kD, and 30 kD PEG, as well as other polymers;
- dextran;

and other molecules known in the art to provide extended half-life and/or protection from proteolytic degradation or clearance.

An Fc domain is the preferred vehicle. The Fc domain may be fused to the N or C termini of the peptides or at both the N and C termini. Fusion to the N terminus is preferred.

As noted above, Fc variants are suitable vehicles within the scope of this invention. A native Fc may be extensively modified to form an Fc variant in accordance with this invention, provided binding to the salvage receptor is maintained; see, for example WO 97/34631 and WO 96/32478. In such Fc variants, one may remove one or more sites of a native Fc that provide structural features or functional activity not required by the fusion molecules of this invention. One may remove these sites by, for example, substituting or deleting residues, inserting residues into the site, or truncating portions containing the site. The inserted or substituted

residues may also be altered amino acids, such as peptidomimetics or D-amino acids. Fc variants may be desirable for a number of reasons, several of which are described below. Exemplary Fc variants include molecules and sequences in which:

1. Sites involved in disulfide bond formation are removed. Such removal may avoid reaction with other cysteine-containing proteins present in the host cell used to produce the molecules of the invention. For this purpose, the cysteine-containing segment at the N-terminus may be truncated or cysteine residues may be deleted or substituted with other amino acids (e.g., alanyl, seryl). In particular, one may truncate the N-terminal 20-amino acid segment of SEQ ID NO: 2 or delete or substitute the cysteine residues at positions 7 and 10 of SEQ ID NO: 2. Even when cysteine residues are removed, the single chain Fc domains can still form a dimeric Fc domain that is held together non-covalently.
2. A native Fc is modified to make it more compatible with a selected host cell. For example, one may remove the PA sequence near the N-terminus of a typical native Fc, which may be recognized by a digestive enzyme in E. coli such as proline iminopeptidase. One may also add an N-terminal methionine residue, especially when the molecule is expressed recombinantly in a bacterial cell such as E. coli. The Fc domain of SEQ ID NO: 2 is one such Fc variant.
3. A portion of the N-terminus of a native Fc is removed to prevent N-terminal heterogeneity when expressed in a selected host cell. For this purpose, one may delete any of the first 20 amino acid residues at the N-terminus, particularly those at positions 1, 2, 3, 4 and 5.
4. One or more glycosylation sites are removed. Residues that are typically glycosylated (e.g., asparagine) may confer cytolytic response. Such residues may be deleted or substituted with unglycosylated residues (e.g., alanine).

5. Sites involved in interaction with complement, such as the C1q binding site, are removed. For example, one may delete or substitute the EKK sequence of human IgG1. Complement recruitment may not be advantageous for the molecules of this invention and so may be avoided with such an Fc variant.
6. Sites are removed that affect binding to Fc receptors other than a salvage receptor. A native Fc may have sites for interaction with certain white blood cells that are not required for the fusion molecules of the present invention and so may be removed.
7. The ADCC site is removed. ADCC sites are known in the art; see, for example, Molec. Immunol. 29 (5): 633-9 (1992) with regard to ADCC sites in IgG1. These sites, as well, are not required for the fusion molecules of the present invention and so may be removed.
8. When the native Fc is derived from a non-human antibody, the native Fc may be humanized. Typically, to humanize a native Fc, one will substitute selected residues in the non-human native Fc with residues that are normally found in human native Fc. Techniques for antibody humanization are well known in the art.

Preferred Fc variants include the following. In SEQ ID NO: 2 (Figure 3), the leucine at position 15 may be substituted with glutamate; the glutamate at position 99, with alanine; and the lysines at positions 101 and 103, with alanines. In addition, one or more tyrosine residues can be replaced by phenyalanine residues.

An alternative vehicle would be a protein, polypeptide, peptide, antibody, antibody fragment, or small molecule (e.g., a peptidomimetic compound) capable of binding to a salvage receptor. For example, one could use as a vehicle a polypeptide as described in U.S. Pat. No. 5,739,277, issued April 14, 1998 to Presta et al. Peptides could also be selected by phage display or RNA-peptide screening for binding to the

FcRn salvage receptor. Such salvage receptor-binding compounds are also included within the meaning of "vehicle" and are within the scope of this invention. Such vehicles should be selected for increased half-life (e.g., by avoiding sequences recognized by proteases) and decreased immunogenicity (e.g., by favoring non-immunogenic sequences, as discovered in antibody humanization).

As noted above, polymer vehicles may also be used for V^1. Various means for attaching chemical moieties useful as vehicles are currently available, see, e.g., Patent Cooperation Treaty ("PCT") International Publication No. WO 96/11953, entitled "N-Terminally Chemically Modified Protein Compositions and Methods," herein incorporated by reference in its entirety. This PCT publication discloses, among other things, the selective attachment of water soluble polymers to the N-terminus of proteins.

A preferred polymer vehicle is polyethylene glycol (PEG). The PEG group may be of any convenient molecular weight and may be linear or branched. The average molecular weight of the PEG will preferably range from about 2 kiloDalton ("kD") to about 100 kD, more preferably from about 5 kD to about 50 kD, most preferably from about 5 kD to about 10 kD. The PEG groups will generally be attached to the compounds of the invention via acylation or reductive alkylation through a reactive group on the PEG moiety (e.g., an aldehyde, amino, thiol, or ester group) to a reactive group on the inventive compound (e.g., an aldehyde, amino, or ester group).

A useful strategy for the PEGylation of synthetic peptides consists of combining, through forming a conjugate linkage in solution, a peptide and a PEG moiety, each bearing a special functionality that is mutually reactive toward the other. The peptides can be easily prepared with conventional solid phase synthesis. The peptides are "preactivated" with

an appropriate functional group at a specific site. The precursors are purified and fully characterized prior to reacting with the PEG moiety. Ligation of the peptide with PEG usually takes place in aqueous phase and can be easily monitored by reverse phase analytical HPLC. The PEGylated peptides can be easily purified by preparative HPLC and characterized by analytical HPLC, amino acid analysis and laser desorption mass spectrometry.

Polysaccharide polymers are another type of water soluble polymer which may be used for protein modification. Dextrans are polysaccharide polymers comprised of individual subunits of glucose predominantly linked by α1-6 linkages. The dextran itself is available in many molecular weight ranges, and is readily available in molecular weights from about 1 kD to about 70 kD. Dextran is a suitable water soluble polymer for use in the present invention as a vehicle by itself or in combination with another vehicle (e.g., Fc). See, for example, WO 96/11953 and WO 96/05309. The use of dextran conjugated to therapeutic or diagnostic immunoglobulins has been reported; see, for example, European Patent Publication No. 0 315 456, which is hereby incorporated by reference in its entirety. Dextran of about 1 kD to about 20 kD is preferred when dextran is used as a vehicle in accordance with the present invention.

Linkers. Any "linker" group is optional. When present, its chemical structure is not critical, since it serves primarily as a spacer. The linker is preferably made up of amino acids linked together by peptide bonds. Thus, in preferred embodiments, the linker is made up of from 1 to 30 amino acids linked by peptide bonds, wherein the amino acids are selected from the 20 naturally occurring amino acids. Some of these amino acids may be glycosylated, as is well understood by those in the art. In a more preferred embodiment, the 1 to 20 amino acids are selected from glycine, alanine, proline, asparagine, glutamine, and lysine. Even more preferably,

a linker is made up of a majority of amino acids that are sterically unhindered, such as glycine and alanine. Thus, preferred linkers are polyglycines (particularly $(Gly)_4$, $(Gly)_5$), poly(Gly-Ala), and polyalanines. Other specific examples of linkers are:

$(Gly)_3Lys(Gly)_4$ (SEQ ID NO: 40);

$(Gly)_3AsnGlySer(Gly)_2$ (SEQ ID NO: 41);

$(Gly)_3Cys(Gly)_4$ (SEQ ID NO: 42); and

GlyProAsnGlyGly (SEQ ID NO: 43).

To explain the above nomenclature, for example, $(Gly)_3Lys(Gly)_4$ means Gly-Gly-Gly-Lys-Gly-Gly-Gly-Gly (SEQ ID NO: 40). Combinations of Gly and Ala are also preferred. The linkers shown here are exemplary; linkers within the scope of this invention may be much longer and may include other residues.

Preferred linkers are amino acid linkers comprising greater than 5 amino acids, with suitable linkers having up to about 500 amino acids selected from glycine, alanine, proline, asparagine, glutamine, lysine, threonine, serine or aspartate. Linkers of about 20 to 50 amino acids are most preferred. One group of preferred linkers are those of the formulae

$GSGSATGGSGSTASSGSGSATx^1x^2$

(SEQ ID NO: 193)

and

$GSGSATGGSGSTASSGSGSATx^1x^2GSGSATGGSGSTASSGSGSATx^3x^4$

(SEQ ID NO: 194)

wherein x^1 and x^3 are each independently basic or hydrophobic residues and x^2 and x^4 are each independently hydrophobic residues. Specific preferred linkers are:

GSGSATGGSGSTASSGSGSATHM

(SEQ ID NO: 59)

GSGSATGGSGSTASSGSGSATGM

(SEQ ID NO: 190)

GSGSATGGSGSTASSGSGSATGS

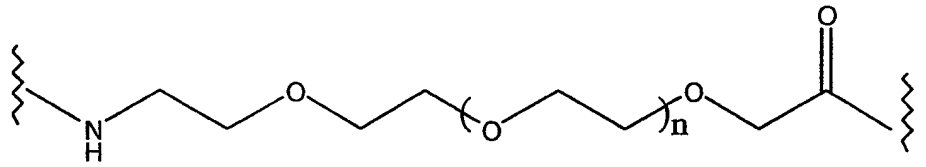
(SEQ ID NO: 191), and

GSGSATGGSGSTASSGSGSATHMGSGSATGGSGSTASSGSGSATHM

(SEQ ID NO: 192).

Non-peptide linkers are also possible. For example, alkyl linkers such as -NH-$(CH_2)_s$-C(O)-, wherein s = 2-20 could be used. These alkyl linkers may further be substituted by any non-sterically hindering group such as lower alkyl (e.g., C_1-C_6) lower acyl, halogen (e.g., Cl, Br), CN, NH_2, phenyl, etc. An exemplary non-peptide linker is a PEG linker,

VII



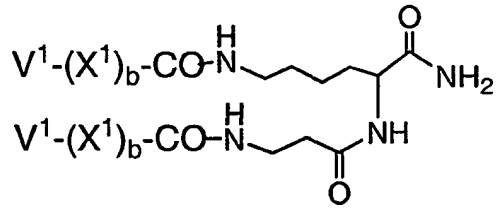
wherein n is such that the linker has a molecular weight of 100 to 5000 kD, preferably 100 to 500 kD. The peptide linkers may be altered to form derivatives in the same manner as described above.

Derivatives. The inventors also contemplate derivatizing the peptide and/or vehicle portion of the compounds. Such derivatives may improve the solubility, absorption, biological half life, and the like of the compounds. The moieties may alternatively eliminate or attenuate any undesirable side-effect of the compounds and the like. Exemplary derivatives include compounds in which:

1. The compound or some portion thereof is cyclic. For example, the peptide portion may be modified to contain two or more Cys residues (e.g., in the linker), which could cyclize by disulfide bond formation.

2. The compound is cross-linked or is rendered capable of cross-linking between molecules. For example, the peptide portion may be modified to contain one Cys residue and thereby be able to form an intermolecular disulfide bond with a like molecule. The compound may also be cross-linked through its C-terminus, as in the molecule shown below.

VIII



In Formula VIII, each "V^1" may represent typically one strand of the Fc domain.

3. One or more peptidyl [-C(O)NR-] linkages (bonds) is replaced by a non-peptidyl linkage. Exemplary non-peptidyl linkages are -CH_2-carbamate [-CH_2-OC(O)NR-], phosphonate , -CH_2-sulfonamide [-CH_2-$S(O)_2$NR-], urea [-NHC(O)NH-], -CH_2-secondary amine, and alkylated peptide [-C(O)NR^6- wherein R^6 is lower alkyl].

4. The N-terminus is derivatized. Typically, the N-terminus may be acylated or modified to a substituted amine. Exemplary N-terminal derivative groups include -NRR^1 (other than -NH_2), -$NRC(O)R^1$, -$NRC(O)OR^1$, -$NRS(O)_2R^1$, -$NHC(O)NHR^1$, succinimide, or benzyloxycarbonyl-NH- (CBZ-NH-), wherein R and R^1 are each independently hydrogen or lower alkyl and wherein the phenyl ring may be substituted with 1 to 3 substituents selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, chloro, and bromo.

5. The free C-terminus is derivatized. Typically, the C-terminus is esterified or amidated. Exemplary C-terminal derivative groups include, for example, -$C(O)R^2$ wherein R^2 is lower alkoxy or -NR^3R^4

wherein R^3 and R^4 are independently hydrogen or C_1-C_8 alkyl (preferably C_1-C_4 alkyl).

6. A disulfide bond is replaced with another, preferably more stable, cross-linking moiety (e.g., an alkylene). See, e.g., Bhatnagar et al. (1996), J. Med. Chem. 39: 3814-9; Alberts et al. (1993) Thirteenth Am. Pep. Symp., 357-9.
7. One or more individual amino acid residues is modified. Various derivatizing agents are known to react specifically with selected sidechains or terminal residues, as described in detail below.

Lysinyl residues and amino terminal residues may be reacted with succinic or other carboxylic acid anhydrides, which reverse the charge of the lysinyl residues. Other suitable reagents for derivatizing alpha-amino-containing residues include imidoesters such as methyl picolinimidate; pyridoxal phosphate; pyridoxal; chloroborohydride; trinitrobenzenesulfonic acid; O-methylisourea; 2,4 pentanedione; and transaminase-catalyzed reaction with glyoxylate.

Arginyl residues may be modified by reaction with any one or combination of several conventional reagents, including phenylglyoxal, 2,3-butanedione, 1,2-cyclohexanedione, and ninhydrin. Derivatization of arginyl residues requires that the reaction be performed in alkaline conditions because of the high pKa of the guanidine functional group. Furthermore, these reagents may react with the groups of lysine as well as the arginine epsilon-amino group.

Specific modification of tyrosyl residues has been studied extensively, with particular interest in introducing spectral labels into tyrosyl residues by reaction with aromatic diazonium compounds or tetranitromethane. Most commonly, N-acetylimidizole and tetranitromethane are used to form O-acetyl tyrosyl species and 3-nitro derivatives, respectively.

Carboxyl sidechain groups (aspartyl or glutamyl) may be selectively modified by reaction with carbodiimides (R'-N=C=N-R') such as 1-cyclohexyl-3-(2-morpholinyl-(4-ethyl) carbodiimide or 1-ethyl-3-(4-azonia-4,4-dimethylpentyl) carbodiimide. Furthermore, aspartyl and glutamyl residues may be converted to asparaginyl and glutaminyl residues by reaction with ammonium ions.

Glutaminyl and asparaginyl residues may be deamidated to the corresponding glutamyl and aspartyl residues. Alternatively, these residues are deamidated under mildly acidic conditions. Either form of these residues falls within the scope of this invention.

Cysteinyl residues can be replaced by amino acid residues or other moieties either to eliminate disulfide bonding or, conversely, to stabilize cross-linking. See, e.g., Bhatnagar et al. (1996), J. Med. Chem. 39: 3814-9.

Derivatization with bifunctional agents is useful for cross-linking the peptides or their functional derivatives to a water-insoluble support matrix or to other macromolecular vehicles. Commonly used cross-linking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), and bifunctional maleimides such as bis-N-maleimido-1,8-octane. Derivatizing agents such as methyl-3-[(p-azidophenyl)dithio]propioimidate yield photoactivatable intermediates that are capable of forming cross-links in the presence of light. Alternatively, reactive water-insoluble matrices such as cyanogen bromide-activated carbohydrates and the reactive substrates described in U.S. Pat. Nos. 3,969,287; 3,691,016; 4,195,128; 4,247,642; 4,229,537; and 4,330,440 are employed for protein immobilization.

Carbohydrate (oligosaccharide) groups may conveniently be attached to sites that are known to be glycosylation sites in proteins.

Generally, O-linked oligosaccharides are attached to serine (Ser) or threonine (Thr) residues while N-linked oligosaccharides are attached to asparagine (Asn) residues when they are part of the sequence Asn-X-Ser/Thr, where X can be any amino acid except proline. X is preferably one of the 19 naturally occurring amino acids other than proline. The structures of N-linked and O-linked oligosaccharides and the sugar residues found in each type are different. One type of sugar that is commonly found on both is N-acetylneuraminic acid (referred to as sialic acid). Sialic acid is usually the terminal residue of both N-linked and O-linked oligosaccharides and, by virtue of its negative charge, may confer acidic properties to the glycosylated compound. Such site(s) may be incorporated in the linker of the compounds of this invention and are preferably glycosylated by a cell during recombinant production of the polypeptide compounds (e.g., in mammalian cells such as CHO, BHK, COS). However, such sites may further be glycosylated by synthetic or semi-synthetic procedures known in the art.

Other possible modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, oxidation of the sulfur atom in Cys, methylation of the alpha-amino groups of lysine, arginine, and histidine side chains. Creighton, Proteins: Structure and Molecule Properties (W. H. Freeman & Co., San Francisco), pp. 79-86 (1983).

Compounds of the present invention may be changed at the DNA level, as well. The DNA sequence of any portion of the compound may be changed to codons more compatible with the chosen host cell. For E. coli, which is the preferred host cell, optimized codons are known in the art. Codons may be substituted to eliminate restriction sites or to include silent restriction sites, which may aid in processing of the DNA in the selected

host cell. The vehicle, linker and peptide DNA sequences may be modified to include any of the foregoing sequence changes.

Methods of Making

The compounds of this invention largely may be made in transformed host cells using recombinant DNA techniques. To do so, a recombinant DNA molecule coding for the peptide is prepared. Methods of preparing such DNA molecules are well known in the art. For instance, sequences coding for the peptides could be excised from DNA using suitable restriction enzymes. Alternatively, the DNA molecule could be synthesized using chemical synthesis techniques, such as the phosphoramidate method. Also, a combination of these techniques could be used.

The invention also includes a vector capable of expressing the peptides in an appropriate host. The vector comprises the DNA molecule that codes for the peptides operatively linked to appropriate expression control sequences. Methods of effecting this operative linking, either before or after the DNA molecule is inserted into the vector, are well known. Expression control sequences include promoters, activators, enhancers, operators, ribosomal binding sites, start signals, stop signals, cap signals, polyadenylation signals, and other signals involved with the control of transcription or translation.

The resulting vector having the DNA molecule thereon is used to transform an appropriate host. This transformation may be performed using methods well known in the art.

Any of a large number of available and well-known host cells may be used in the practice of this invention. The selection of a particular host is dependent upon a number of factors recognized by the art. These include, for example, compatibility with the chosen expression vector, toxicity of the peptides encoded by the DNA molecule, rate of

transformation, ease of recovery of the peptides, expression characteristics, bio-safety and costs. A balance of these factors must be struck with the understanding that not all hosts may be equally effective for the expression of a particular DNA sequence. Within these general guidelines, useful microbial hosts include bacteria (such as E. coli sp.), yeast (such as Saccharomyces sp.) and other fungi, insects, plants, mammalian (including human) cells in culture, or other hosts known in the art.

Next, the transformed host is cultured and purified. Host cells may be cultured under conventional fermentation conditions so that the desired compounds are expressed. Such fermentation conditions are well known in the art. Finally, the peptides are purified from culture by methods well known in the art.

The compounds may also be made by synthetic methods. For example, solid phase synthesis techniques may be used. Suitable techniques are well known in the art, and include those described in Merrifield (1973), Chem. Polypeptides, pp. 335-61 (Katsoyannis and Panayotis eds.); Merrifield (1963), J. Am. Chem. Soc. 85: 2149; Davis et al. (1985), Biochem. Intl. 10: 394-414; Stewart and Young (1969), Solid Phase Peptide Synthesis; U.S. Pat. No. 3,941,763; Finn et al. (1976), The Proteins (3rd ed.) 2: 105-253; and Erickson et al. (1976), The Proteins (3rd ed.) 2: 257-527. Solid phase synthesis is the preferred technique of making individual peptides since it is the most cost-effective method of making small peptides.

Compounds that contain derivatized peptides or which contain non-peptide groups may be synthesized by well-known organic chemistry techniques.

Uses of the Compounds

Compounds of this invention may be particularly useful in treatment of B-cell mediated autoimmune diseases. In particular, the

compounds of this invention may be useful in treating, preventing, ameliorating, diagnosing or prognosing lupus, including systemic lupus erythematosus (SLE), and lupus-associated diseases and conditions. Other preferred indications include B-cell mediated cancers, including B-cell lymphoma.

The compounds of this invention can also be used to treat inflammatory conditions of the joints. Inflammatory conditions of a joint are chronic joint diseases that afflict and disable, to varying degrees, millions of people worldwide. Rheumatoid arthritis is a disease of articular joints in which the cartilage and bone are slowly eroded away by a proliferative, invasive connective tissue called pannus, which is derived from the synovial membrane. The disease may involve peri-articular structures such as bursae, tendon sheaths and tendons as well as extra-articular tissues such as the subcutis, cardiovascular system, lungs, spleen, lymph nodes, skeletal muscles, nervous system (central and peripheral) and eyes (Silberberg (1985), Anderson's Pathology, Kissane (ed.), II:1828). Osteoarthritis is a common joint disease characterized by degenerative changes in articular cartilage and reactive proliferation of bone and cartilage around the joint. Osteoarthritis is a cell-mediated active process that may result from the inappropriate response of chondrocytes to catabolic and anabolic stimuli. Changes in some matrix molecules of articular cartilage reportedly occur in early osteoarthritis (Thonar et al. (1993), Rheumatic disease clinics of North America, Moskowitz (ed.), 19:635-657 and Shinmei et al. (1992), Arthritis Rheum., 35:1304-1308). TALL-1, TALL-1R and modulators thereof are believed to be useful in the treatment of these and related conditions.

Compounds of this invention may also be useful in treatment of a number of additional diseases and disorders, including:

- acute pancreatitis;

- ALS;
- Alzheimer's disease;
- asthma;
- atherosclerosis;
- autoimmune hemolytic anemia;
- cancer, particularly cancers related to B cells;
- cachexia/anorexia;
- chronic fatigue syndrome;
- cirrhosis (e.g., primary biliary cirrhosis);
- diabetes (e.g., insulin diabetes);
- fever;
- glomerulonephritis, including IgA glomerulonephritis and primary glomerulonephritis;
- Goodpasture's syndrome;
- Guillain-Barre syndrome;
- graft versus host disease;
- Hashimoto's thyroiditis;
- hemorrhagic shock;
- hyperalgesia;
- inflammatory bowel disease;
- inflammatory conditions of a joint, including osteoarthritis, psoriatic arthritis and rheumatoid arthritis;
- inflammatory conditions resulting from strain, sprain, cartilage damage, trauma, orthopedic surgery, infection or other disease processes;
- insulin-dependent diabetes mellitus;

- ischemic injury, including cerebral ischemia (e.g., brain injury as a result of trauma, epilepsy, hemorrhage or stroke, each of which may lead to neurodegeneration);
- learning impairment;
- lung diseases (e.g., ARDS);
- multiple myeloma;
- multiple sclerosis;
- Myasthenia gravis;
- myelogenous (e.g., AML and CML) and other leukemias;
- myopathies (e.g., muscle protein metabolism, esp. in sepsis);
- neurotoxicity (e.g., as induced by HIV);
- osteoporosis;
- pain;
- Parkinson's disease;
- Pemphigus;
- polymyositis/dermatomyositis;
- pulmonary inflammation, including autoimmune pulmonary inflammation;
- pre-term labor;
- psoriasis;
- Reiter's disease;
- reperfusion injury;
- septic shock;
- side effects from radiation therapy;
- Sjogren's syndrome;
- sleep disturbance;
- temporal mandibular joint disease;

- thrombocytopenia, including idiopathic thrombocytopenia and autoimmune neonatal thrombocytopenia;
- tumor metastasis;
- uveitis; and
- vasculitis.

Compounds of this invention may be administered alone or in combination with a therapeutically effective amount of other drugs, including analgesic agents, disease-modifying anti-rheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs), and any immune and/or inflammatory modulators. Thus, compounds of this invention may be administered with:

- Modulators of other members of the TNF/TNF receptor family, including TNF antagonists, such as etanercept (Enbrel™), sTNF-RI, onercept, D2E7, and Remicade™.
- Nerve growth factor (NGF) modulators.
- IL-1 inhibitors, including IL-1ra molecules such as anakinra and more recently discovered IL-1ra-like molecules such as IL-1Hy1 and IL-1Hy2; IL-1 "trap" molecules as described in U.S. Pat. No. 5,844,099, issued December 1, 1998; IL-1 antibodies; solubilized IL-1 receptor, and the like.
- IL-6 inhibitors (e.g., antibodies to IL-6).
- IL-8 inhibitors (e.g., antibodies to IL-8).
- IL-18 inhibitors (e.g., IL-18 binding protein, solubilized IL-18 receptor, or IL-18 antibodies).
- Interleukin-1 converting enzyme (ICE) modulators.
- insulin-like growth factors (IGF-1, IGF-2) and modulators thereof.
- Transforming growth factor-β (TGF-β), TGF-β family members, and TGF-β modulators.

- Fibroblast growth factors FGF-1 to FGF-10, and FGF modulators.
- Osteoprotegerin (OPG), OPG analogues, osteoprotective agents, and antibodies to OPG-ligand (OPG-L).
- bone anabolic agents, such as parathyroid hormone (PTH), PTH fragments, and molecules incorporating PTH fragments (e.g., PTH (1-34)-Fc).
- PAF antagonists.
- Keratinocyte growth factor (KGF), KGF-related molecules (e.g., KGF-2), and KGF modulators.
- COX-2 inhibitors, such as Celebrex™ and Vioxx™.
- Prostaglandin analogs (e.g., E series prostaglandins).
- Matrix metalloproteinase (MMP) modulators.
- Nitric oxide synthase (NOS) modulators, including modulators of inducible NOS.
- Modulators of glucocorticoid receptor.
- Modulators of glutamate receptor.
- Modulators of lipopolysaccharide (LPS) levels.
- Anti-cancer agents, including inhibitors of oncogenes (e.g., fos, jun) and interferons.
- Noradrenaline and modulators and mimetics thereof.

Pharmaceutical Compositions

In General. The present invention also provides methods of using pharmaceutical compositions of the inventive compounds. Such pharmaceutical compositions may be for administration for injection, or for oral, pulmonary, nasal, transdermal or other forms of administration. In general, the invention encompasses pharmaceutical compositions comprising effective amounts of a compound of the invention together with pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. Such compositions include diluents of various buffer content (e.g., Tris-HCl, acetate, phosphate), pH and ionic strength; additives such as detergents and solubilizing agents (e.g., Tween 80, Polysorbate 80), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimersol, benzyl alcohol) and bulking substances (e.g., lactose, mannitol); incorporation of the material into particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, etc. or into liposomes. Hyaluronic acid may also be used, and this may have the effect of promoting sustained duration in the circulation. Such compositions may influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of the present proteins and derivatives. See, e.g., Remington's Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, PA 18042) pages 1435-1712 which are herein incorporated by reference in their entirety. The compositions may be prepared in liquid form, or may be in dried powder, such as lyophilized form. Implantable sustained release formulations are also contemplated, as are transdermal formulations.

Oral dosage forms. Contemplated for use herein are oral solid dosage forms, which are described generally in Chapter 89 of Remington's Pharmaceutical Sciences (1990), 18th Ed., Mack Publishing Co. Easton PA 18042, which is herein incorporated by reference in its entirety. Solid dosage forms include tablets, capsules, pills, troches or lozenges, cachets

or pellets. Also, liposomal or proteinoid encapsulation may be used to formulate the present compositions (as, for example, proteinoid microspheres reported in U.S. Patent No. 4,925,673). Liposomal encapsulation may be used and the liposomes may be derivatized with various polymers (e.g., U.S. Patent No. 5,013,556). A description of possible solid dosage forms for the therapeutic is given in Chapter 10 of Marshall, K., Modern Pharmaceutics (1979), edited by G. S. Banker and C. T. Rhodes, herein incorporated by reference in its entirety. In general, the formulation will include the inventive compound, and inert ingredients which allow for protection against the stomach environment, and release of the biologically active material in the intestine.

Also specifically contemplated are oral dosage forms of the above inventive compounds. If necessary, the compounds may be chemically modified so that oral delivery is efficacious. Generally, the chemical modification contemplated is the attachment of at least one moiety to the compound molecule itself, where said moiety permits (a) inhibition of proteolysis; and (b) uptake into the blood stream from the stomach or intestine. Also desired is the increase in overall stability of the compound and increase in circulation time in the body. Moieties useful as covalently attached vehicles in this invention may also be used for this purpose. Examples of such moieties include: PEG, copolymers of ethylene glycol and propylene glycol, carboxymethyl cellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone and polyproline. See, for example, Abuchowski and Davis, Soluble Polymer-Enzyme Adducts, Enzymes as Drugs (1981), Hocenberg and Roberts, eds., Wiley-Interscience, New York, NY, , pp. 367-83; Newmark, et al. (1982), J. Appl. Biochem. 4:185-9. Other polymers that could be used are poly-1,3-dioxolane and poly-1,3,6-tioxocane. Preferred for pharmaceutical usage, as indicated above, are PEG moieties.

For oral delivery dosage forms, it is also possible to use a salt of a modified aliphatic amino acid, such as sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC), as a carrier to enhance absorption of the therapeutic compounds of this invention. The clinical efficacy of a heparin formulation using SNAC has been demonstrated in a Phase II trial conducted by Emisphere Technologies. See US Patent No. 5,792,451, "Oral drug delivery composition and methods".

The compounds of this invention can be included in the formulation as fine multiparticulates in the form of granules or pellets of particle size about 1 mm. The formulation of the material for capsule administration could also be as a powder, lightly compressed plugs or even as tablets. The therapeutic could be prepared by compression.

Colorants and flavoring agents may all be included. For example, the protein (or derivative) may be formulated (such as by liposome or microsphere encapsulation) and then further contained within an edible product, such as a refrigerated beverage containing colorants and flavoring agents.

One may dilute or increase the volume of the compound of the invention with an inert material. These diluents could include carbohydrates, especially mannitol, α-lactose, anhydrous lactose, cellulose, sucrose, modified dextrans and starch. Certain inorganic salts may also be used as fillers including calcium triphosphate, magnesium carbonate and sodium chloride. Some commercially available diluents are Fast-Flo, Emdex, STA-Rx 1500, Emcompress and Avicell.

Disintegrants may be included in the formulation of the therapeutic into a solid dosage form. Materials used as disintegrants include but are not limited to starch including the commercial disintegrant based on starch, Explotab. Sodium starch glycolate, Amberlite, sodium carboxymethylcellulose, ultramylopectin, sodium alginate, gelatin, orange

peel, acid carboxymethyl cellulose, natural sponge and bentonite may all be used. Another form of the disintegrants are the insoluble cationic exchange resins. Powdered gums may be used as disintegrants and as binders and these can include powdered gums such as agar, Karaya or tragacanth. Alginic acid and its sodium salt are also useful as disintegrants.

Binders may be used to hold the therapeutic agent together to form a hard tablet and include materials from natural products such as acacia, tragacanth, starch and gelatin. Others include methyl cellulose (MC), ethyl cellulose (EC) and carboxymethyl cellulose (CMC). Polyvinyl pyrrolidone (PVP) and hydroxypropylmethyl cellulose (HPMC) could both be used in alcoholic solutions to granulate the therapeutic.

An antifrictional agent may be included in the formulation of the therapeutic to prevent sticking during the formulation process. Lubricants may be used as a layer between the therapeutic and the die wall, and these can include but are not limited to; stearic acid including its magnesium and calcium salts, polytetrafluoroethylene (PTFE), liquid paraffin, vegetable oils and waxes. Soluble lubricants may also be used such as sodium lauryl sulfate, magnesium lauryl sulfate, polyethylene glycol of various molecular weights, Carbowax 4000 and 6000.

Glidants that might improve the flow properties of the drug during formulation and to aid rearrangement during compression might be added. The glidants may include starch, talc, pyrogenic silica and hydrated silicoaluminate.

To aid dissolution of the compound of this invention into the aqueous environment a surfactant might be added as a wetting agent. Surfactants may include anionic detergents such as sodium lauryl sulfate, dioctyl sodium sulfosuccinate and dioctyl sodium sulfonate. Cationic detergents might be used and could include benzalkonium chloride or

benzethonium chloride. The list of potential nonionic detergents that could be included in the formulation as surfactants are lauromacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 50 and 60, glycerol monostearate, polysorbate 40, 60, 65 and 80, sucrose fatty acid ester, methyl cellulose and carboxymethyl cellulose. These surfactants could be present in the formulation of the protein or derivative either alone or as a mixture in different ratios.

Additives may also be included in the formulation to enhance uptake of the compound. Additives potentially having this property are for instance the fatty acids oleic acid, linoleic acid and linolenic acid.

Controlled release formulation may be desirable. The compound of this invention could be incorporated into an inert matrix which permits release by either diffusion or leaching mechanisms; e.g., gums. Slowly degenerating matrices may also be incorporated into the formulation, e.g., alginates, polysaccharides. Another form of a controlled release of the compounds of this invention is by a method based on the Oros therapeutic system (Alza Corp.), i.e., the drug is enclosed in a semipermeable membrane which allows water to enter and push drug out through a single small opening due to osmotic effects. Some enteric coatings also have a delayed release effect.

Other coatings may be used for the formulation. These include a variety of sugars which could be applied in a coating pan. The therapeutic agent could also be given in a film coated tablet and the materials used in this instance are divided into 2 groups. The first are the nonenteric materials and include methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, methylhydroxy-ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl-methyl cellulose, sodium carboxy-methyl cellulose, providone and the polyethylene glycols. The second group consists of the enteric materials that are commonly esters of phthalic acid.

A mix of materials might be used to provide the optimum film coating. Film coating may be carried out in a pan coater or in a fluidized bed or by compression coating.

Pulmonary delivery forms. Also contemplated herein is pulmonary delivery of the present protein (or derivatives thereof). The protein (or derivative) is delivered to the lungs of a mammal while inhaling and traverses across the lung epithelial lining to the blood stream. (Other reports of this include Adjei et al., Pharma. Res. (1990) 7: 565-9; Adjei et al. (1990), Internatl. J. Pharmaceutics 63: 135-44 (leuprolide acetate); Braquet et al. (1989), J. Cardiovasc. Pharmacol. 13 (suppl.5): s.143-146 (endothelin-1); Hubbard et al. (1989), Annals Int. Med. 3: 206-12 (α1-antitrypsin); Smith et al. (1989), J. Clin. Invest. 84: 1145-6 (α1-proteinase); Oswein et al. (March 1990), "Aerosolization of Proteins", Proc. Symp. Resp. Drug Delivery II, Keystone, Colorado (recombinant human growth hormone); Debs et al. (1988), J. Immunol. 140: 3482-8 (interferon-γ and tumor necrosis factor α) and Platz et al., U.S. Patent No. 5,284,656 (granulocyte colony stimulating factor).

Contemplated for use in the practice of this invention are a wide range of mechanical devices designed for pulmonary delivery of therapeutic products, including but not limited to nebulizers, metered dose inhalers, and powder inhalers, all of which are familiar to those skilled in the art. Some specific examples of commercially available devices suitable for the practice of this invention are the Ultravent nebulizer, manufactured by Mallinckrodt, Inc., St. Louis, Missouri; the Acorn II nebulizer, manufactured by Marquest Medical Products, Englewood, Colorado; the Ventolin metered dose inhaler, manufactured by Glaxo Inc., Research Triangle Park, North Carolina; and the Spinhaler powder inhaler, manufactured by Fisons Corp., Bedford, Massachusetts.

All such devices require the use of formulations suitable for the dispensing of the inventive compound. Typically, each formulation is specific to the type of device employed and may involve the use of an appropriate propellant material, in addition to diluents, adjuvants and/or carriers useful in therapy.

The inventive compound should most advantageously be prepared in particulate form with an average particle size of less than 10 μm (or microns), most preferably 0.5 to 5 μm, for most effective delivery to the distal lung.

Pharmaceutically acceptable carriers include carbohydrates such as trehalose, mannitol, xylitol, sucrose, lactose, and sorbitol. Other ingredients for use in formulations may include DPPC, DOPE, DSPC and DOPC. Natural or synthetic surfactants may be used. PEG may be used (even apart from its use in derivatizing the protein or analog). Dextrans, such as cyclodextran, may be used. Bile salts and other related enhancers may be used. Cellulose and cellulose derivatives may be used. Amino acids may be used, such as use in a buffer formulation.

Also, the use of liposomes, microcapsules or microspheres, inclusion complexes, or other types of carriers is contemplated.

Formulations suitable for use with a nebulizer, either jet or ultrasonic, will typically comprise the inventive compound dissolved in water at a concentration of about 0.1 to 25 mg of biologically active protein per mL of solution. The formulation may also include a buffer and a simple sugar (e.g., for protein stabilization and regulation of osmotic pressure). The nebulizer formulation may also contain a surfactant, to reduce or prevent surface induced aggregation of the protein caused by atomization of the solution in forming the aerosol.

Formulations for use with a metered-dose inhaler device will generally comprise a finely divided powder containing the inventive

compound suspended in a propellant with the aid of a surfactant. The propellant may be any conventional material employed for this purpose, such as a chlorofluorocarbon, a hydrochlorofluorocarbon, a hydrofluorocarbon, or a hydrocarbon, including trichlorofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethanol, and 1,1,1,2-tetrafluoroethane, or combinations thereof. Suitable surfactants include sorbitan trioleate and soya lecithin. Oleic acid may also be useful as a surfactant.

Formulations for dispensing from a powder inhaler device will comprise a finely divided dry powder containing the inventive compound and may also include a bulking agent, such as lactose, sorbitol, sucrose, mannitol, trehalose, or xylitol in amounts which facilitate dispersal of the powder from the device, e.g., 50 to 90% by weight of the formulation.

Nasal delivery forms. Nasal delivery of the inventive compound is also contemplated. Nasal delivery allows the passage of the protein to the blood stream directly after administering the therapeutic product to the nose, without the necessity for deposition of the product in the lung. Formulations for nasal delivery include those with dextran or cyclodextran. Delivery via transport across other mucous membranes is also contemplated.

Dosages. The dosage regimen involved in a method for treating the above-described conditions will be determined by the attending physician, considering various factors which modify the action of drugs, e.g. the age, condition, body weight, sex and diet of the patient, the severity of any infection, time of administration and other clinical factors. Generally, the daily regimen should be in the range of 0.1-1000 micrograms of the inventive compound per kilogram of body weight, preferably 0.1-150 micrograms per kilogram.

Specific preferred embodiments

The inventors have determined preferred structures for the preferred peptides listed in Table 4 below. The symbol "Λ" may be any of the linkers described herein or may simply represent a normal peptide bond (i.e., so that no linker is present). Tandem repeats and linkers are shown separated by dashes for clarity.

Table 4—Preferred embodiments

Sequence/structure	SEQ ID NO:
LPGCKWDLLIKQWVCDPL-Λ-V^1	44
V^1-Λ- LPGCKWDLLIKQWVCDPL	45
LPGCKWDLLIKQWVCDPL -Λ- LPGCKWDLLIKQWVCDPL -Λ-V^1	46
V^1-Λ- LPGCKWDLLIKQWVCDPL -Λ- LPGCKWDLLIKQWVCDPL	47
SADCYFDILTKSDVCTSS-Λ-V^1	48
V^1-Λ- SADCYFDILTKSDVCTSS	49
SADCYFDILTKSDVTSS-Λ- SADCYFDILTKSDVTSS -Λ-V^1	50
V^1-Λ- SADCYFDILTKSDVTSS -Λ- SADCYFDILTKSDVTSS	51
FHDCKWDLLTKQWVCHGL-Λ-V^1	52
V^1-Λ- FHDCKWDLLTKQWVCHGL	53
FHDCKWDLLTKQWVCHGL -Λ- FHDCKWDLLTKQWVCHGL -Λ-V^1	54
V^1-Λ- FHDCKWDLLTKQWVCHGL -Λ- FHDCKWDLLTKQWVCHGL	55

"V^1" is an Fc domain as defined previously herein. In addition to those listed in Table 4, the inventors further contemplate heterodimers in which each strand of an Fc dimer is linked to a different peptide sequence; for example, wherein each Fc is linked to a different sequence selected from Table 2.

All of the compounds of this invention can be prepared by methods described in PCT appl. no. WO 99/25044.

The invention will now be further described by the following working examples, which are illustrative rather than limiting.

EXAMPLE 1

Peptides

Peptide Phage Display

1. Magnetic bead preparation

A. Fc-TALL-1 immobilization on magnetic beads

The recombinant Fc-TALL-1 protein was immobilized on the Protein A Dynabeads (Dynal) at a concentration of 8 μg of Fc-TALL-1 per 100 μl of the bead stock from the manufacturer. By drawing the beads to one side of a tube using a magnet and pipetting away the liquid, the beads were washed twice with the phosphate buffer saline (PBS) and resuspended in PBS. The Fc-TALL-1 protein was added to the washed beads at the above concentration and incubated with rotation for 1 hour at room temperature. The Fc-TALL-1 coated beads were then blocked by adding bovine serum albumin (BSA) to 1% final concentration and incubating overnight at 4 °C with rotation. The resulting Fc-TALL-1 coated beads were then washed twice with PBST (PBS with 0.05% Tween-20) before being subjected to the selection procedures.

B. Negative selection bead preparation

Additional beads were also prepared for negative selections. For each panning condition, 250 μl of the bead stock from the manufacturer was subjected to the above procedure (section 1A) except that the incubation step with Fc-TALL-1 was omitted. In the last washing step, the beads were divided into five 50 μl aliquots.

2. Selection of TALL-1 binding phage

A. Overall strategy

Two filamentous phage libraries, TN8-IX ($5X10^9$ independent transformants) and TN12-I ($1.4X10^9$ independent transformants) (Dyax Corp.), were used to select for TALL-1 binding phage. Each library was subjected to either pH 2 elution or 'bead elution' (section 2E). Therefore, four different panning conditions were carried out for the TALL-1 project (TN8-IX using the

pH2 elution method, TN8-IX using the bead elution method, TN12-I the using pH2 elution method, and TN12-I using the bead elution method). Three rounds of selection were performed for each condition.

B. Negative selection

For each panning condition, about 100 random library equivalent ($5X10^{11}$ pfu for TN8-IX and $1.4X10^{11}$ pfu for TN12-I) was aliquoted from the library stock and diluted to 300 µl with PBST. After the last washing liquid was drawn out from the first 50 µl aliquot of the beads prepared for negative selections (section 1B), the 300 µl diluted library stock was added to the beads. The resulting mixture was incubated for 10 minutes at room temperature with rotation. The phage supernatant was drawn out using the magnet and added to the second 50 µl aliquot for another negative selection step. In this way, five negative selection steps were performed.

C. Selection using the Fc-TALL-1 protein coated beads

The phage supernatant after the last negative selection step (section 1B) was added to the Fc-TALL-1 coated beads after the last washing step (section 1A). This mixture was incubated with rotation for two hours at room temperature, allowing specific phage to bind to the target protein. After the supernatant is discarded, the beads were washed seven times with PBST.

D. pH2 elution of bound phage

After the last washing step (section 2C), the bound phages were eluted from the magnetic beads by adding 200 µl of CBST (50 mM sodium citrate, 150 mM sodium chloride, 0.05% Tween-20, pH2). After 5 minute incubation at room temperature, the liquid containing the eluted phage were drawn out and transferred to another tube. The elution step was repeated again by adding 200 µl of CBST and incubating for 5 minutes. The liquids from two elution steps were added together, and 100 µl of 2 M Tris solution (pH 8) was added to neutralize the pH. 500 µl of Min A Salts solution (60 mM K_2HPO_4, 33 mM KH_2PO_4, 7.6 mM $(NH_4)SO_4$, and 1.7 mM sodium citrate) was added to make the final volume to 1 ml.

E. 'bead elution'

After the final washing liquid was drawn out (section 2C), 1 ml of Min A salts solution was added to the beads. This bead mixture was added directly to a concentrated bacteria sample for infection (section 3A and 3B).

3. Amplification

A. Preparation of plating cells

Fresh E. Coli. (XL-1 Blue MRF') culture was grown to OD_{600} = 0.5 in LB media containing 12.5 μg/ml tetracycline. For each panning condition, 20 ml of this culture was chilled on ice and centrifuged. The bacteria pellet was resuspended in 1 ml of the Min A Salts solution.

B. Transduction

Each mixture from different elution methods (section 2D and 2E) was added to a concentrated bacteria sample (section 3A) and incubated at 37 °C for 15 minutes. 2 ml of NZCYM media (2XNZCYM, 50 μg/ml ampicillin) was added to each mixture and incubated at room temperature for 15 minutes. The resulting 4 ml solution was plated on a large NZCYM agar plate containing 50 μg/ml ampicillin and incubated overnight at 37 °C.

C. Phage Harvesting

Each of the bacteria/phage mixture that was grown overnight on a large NZCYM agar plate (section 3B) was scraped off in 35 ml of LB media, and the agar plate was further rinsed with additional 35 ml of LB media. The resulting bacteria/phage mixture in LB media was centrifuged to pellet the bacteria away. 50 ml the of the phage supernatant was transferred to a fresh tube, and 12.5 ml of PEG solution (20% PEG8000, 3.5M ammonium acetate) was added and incubated on ice for 2 hours to precipitate phages. Precipitated phages were centrifuged down and resuspended in 6 ml of the phage resuspension buffer (250 mM NaCl, 100 mM Tris pH8, 1 mM EDTA). This phage solution was further purified by centrifuging away the remaining bacteria and precipitating the phage for the second time by adding 1.5 ml of the PEG solution. After a centrifugation step, the phage pellet was resuspended in 400 μl of PBS. This solution was subjected to a final centrifugation to rid of remaining bacteria debris. The resulting phage

preparation was titered by a standard plaque formation assay (Molecular Cloning, Maniatis et al 3rd Edition).

4. Two more rounds of selection and amplification.

In the second round, the amplified phage (10^{10} pfu) from the first round (section 3C) was used as the input phage to perform the selection and amplification steps (sections 2 and 3). The amplified phage (10^{10} pfu) from the 2nd round in turn was used as the input phage to perform 3rd round of selection and amplification (sections 2 and 3). After the elution steps (sections 2D and 2E) of the 3rd round, a small fraction of the eluted phage was plated out as in the plaque formation assay (section 3C). Individual plaques were picked and placed into 96 well microtiter plates containing 100 µl of TE buffer in each well. These master plates were incubated in a 37 °C incubator for 1 hour to allow phages to elute into the TE buffer.

5. Clonal analysis (Phage ELISA and sequencing)

The phage clones were analyzed by phage ELISA and sequencing methods. The sequences were ranked based on the combined results from these two assays.

A. Phage ELISA

An XL-1 Blue MRF' culture was grown until OD_{600} reaches 0.5. 30 µl of this culture was aliquoted into each well of a 96 well microtiter plate. 10 µl of eluted phage (section 4) was added to each well and allowed to infect bacteria for 15 min at room temperature. 130 µl of LB media containing 12.5 µg/ml of tetracycline and 50 µg/ml of ampicillin was added to each well. The microtiter plate was then incubated overnight at 37 °C. The recombinant TALL-1 protein (1 µg/ml in PBS) was allowed to coat onto the 96-well Maxisorp plates (NUNC) overnight and 4°C. As a control, the recombinant Fc-Trail protein was coated onto a separate Maxisorp plate at the same molar concentration as the TALL-1 protein.

On the following day, liquids in the protein coated Maxisorp plates were discarded, and each well was blocked with 300 µl of 2% BSA solution at 37 °C

for one hour. The BSA solution was discarded, and the wells were washed three times with the PBST solution. After the last washing step, 50 µl of PBST was added to each well of the protein coated Maxisorp plates. Each of the 50 µl overnight cultures in the 96 well microtiter plate was transferred to the corresponding wells of the TALL-1 coated plates as well as the control Fc-Trail coated plates. The 100 µl mixtures in the two kinds of plates were incubated for 1 hour at room temperature. The liquid was discarded from the Maxisorp plates, and the wells were washed five times with PBST. The HRP-conjugated anti-M13 antibody (Pharmacia) was diluted to 1:7,500, and 100 µl of the diluted solution was added to each well of the Maxisorp plates for 1 hour incubation at room temperature. The liquid was again discarded and the wells were washed seven times with PBST. 100 µl of tetramethylbenzidine (TMB) substrate (Sigma) was added to each well for the color reaction to develop, and the reaction was stopped with 50 µl of the 5 N H_2SO_4 solution. The OD_{450} was read on a plate reader (Molecular Devices).

B. Sequencing of the phage clones.

For each phage clone, the sequencing template was prepared by a PCR method. The following oligonucleotide pair was used to amplify about 500 nucleotide fragment:

primer #1 (5'-CGGCGCAACTATCGGTATCAAGCTG-3') (SEQ ID NO: 56) and primer #2 (5'-CATGTACCGTAACACTGAGTTTCGTC-3'). (SEQ ID NO: 57) The following mixture was prepared for each clone.

Reagents	volume (µL) / tube
dH_2O	26.25
50% glycerol	10
10B PCR Buffer (w/o $MgCl_2$)	5
25 mM $MgCl_2$	4
10 mM dNTP mix	1
100 µM primer 1	0.25
100 µM primer 2	0.25
Taq polymerase	0.25
Phage in TE (section 4)	3
Final reaction volume	**50**

The thermocycler (GeneAmp PCR System 9700, Applied Biosystems) was used to run the following program: 94°C for 5 min; [94°C for 30 sec, 55°C for 30 sec, 72°C for 45 sec.]x30 cycles; 72°C for 7 min; cool to 4°C. The PCR product was checked by running 5 μl of each PCR reaction on a 1% agarose gel. The PCR product in the remaining 45 μl from each reaction was cleaned up using the QIAquick Multiwell PCR Purification kit (Qiagen), following the manufacturer's protocol. The resulting product was then sequenced using the ABI 377 Sequencer (Perkin-Elmer) following the manufacturer recommended protocol.

6. Sequence ranking and consensus sequence determination

A. Sequence ranking

The peptide sequences that were translated from variable nucleotide sequences (section 5B) were correlated to ELISA data. The clones that showed high OD_{450} in the TALL-1 coated wells and low OD_{450} in the Fc-Trail coated wells were considered more important. The sequences that occur multiple times were also considered important. Candidate sequences were chosen based on these criteria for further analysis as peptides or peptibodies. Five and nine candidate peptide sequences were selected from the TN8-IX and TN12-I libraries, respectively.

B. Consensus sequence determination

The majority of sequences selected from the TN12-I library contained a very conserved DBL motif. This motif was also observed in sequences selected from the TN8-IB library as well. Another motif, PFPWE (SEQ ID NO: 110) was also observed in sequences obtained from the TN8-IB library.

A consensus peptide, FHDCKWDLLTKQWVCHGL (SEQ ID NO: 58), was designed based on the DBL motif. Since peptides derived from the TN12-I library were the most active ones, the top 26 peptide sequences based on the above ranking criteria (section 5A) were aligned by the DBL motif. The underlined "core amino acid sequence" was obtained by determining the amino acid that occur the most in each position. The two cysteines adjacent to the core

sequences were fixed amino acids in the TN12-I library. The rest of the amino acid sequence in the consensus peptide is taken from one of the candidate peptides, TALL-1-12-10 (Table 2, SEQ ID NO: 37). The peptide and peptibody that was derived from this consensus sequence were most active in the B cell proliferation assay.

EXAMPLE 2

Peptibodies

A set of 12 TALL-1 inhibitory peptibodies (Table 5) was constructed in which a monomer of each peptide was fused in-frame to the Fc region of human IgG1. Each TALL-1 inhibitory peptibody was constructed by annealing the pairs of oligonucleotides shown in Table 6 to generate a duplex encoding the peptide and a linker comprised of 5 glycine residues and one valine residue as an NdeI to SalI fragment. These duplex molecules were ligated into a vector (pAMG21-RANK-Fc, described herein) containing the human Fc gene, also digested with NdeI and SalI. The resulting ligation mixtures were transformed by electroporation into E. coli strain 2596 cells (GM221, described herein). Clones were screened for the ability to produce the recombinant protein product and to possess the gene fusion having the correct nucleotide sequence. A single such clone was selected for each of the peptibodies. The nucleotide and amino acid sequences of the fusion proteins are shown in Figure 4A through 4F.

Table 5. Peptide sequences and oligonucleotides used to generate TALL-1 inhibitory peptibodies.

Peptibody	Peptibody SEQ ID NO	Peptide Sequence	Sense oligo-nucleotide	Antisense oligo-nucleotide
TALL-1-8-1-a	29	PGTCFPFPWECTHA	2517-24	2517-25
TALL-1-8-2-a	30	WGACWPFPWECFKE	2517-26	2517-27
TALL-1-8-4-a	31	VPFCDLLTKHCFEA	2517-28	2517-29
TALL-1-12-4-a	32	GSRCKYKWDVLTKQCFHH	2517-30	2517-31
TALL-1-12-3-a	33	LPGCKWDLLIKQWVCDPL	2517-32	2517-33
TALL-1-12-5-a	34	SADCYFDILTKSDVCTSS	2517-34	2517-35
TALL-1-12-8-a	35	SDDCMYDQLTRMFICSNL	2517-36	2517-37
TALL-1-12-9-a	36	DLNCKYDELTYKEWCQFN	2521-92	2521-93

TALL-1-12-10-a	37	FHDCKYDLLTRQMVCHGL	2521-94	2521-95
TALL-1-12-11-a	38	RNHCFWDHLLKQDICPSP	2521-96	2521-97
TALL-1-12-14-a	39	ANQCWWDSLTKKNVCEFF	2521-98	2521-99
TALL-1-consensus	58	FHDCKWDLLTKQWVCHGL	2551-48	2551-49

Table 5B TALL-1 inhibitory peptibodies.

Peptibody	Peptibody SEQ ID NO	Peptide Sequence
TALL-1-8-1-a	111	MPGTCFPFPW ECTHAGGGGG VDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGK
TALL-1-8-2-a	112	MWGACWPFPW ECFKEGGGGG VDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGK
TALL-1-8-4-a	113	MVPFCDLLTK HCFEAGGGGG VDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGK
TALL-1-12-4-a	114	MGSRCKYKWD VLTKQCFHHG GGGGVDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK
TALL-1-12-3-a	115	MLPGCKWDLL IKQWVCDPLG GGGGVDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK
TALL-1-12-5-a	116	MSADCYFDIL TKSDVCTSSG GGGG VDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK
TALL-1-12-8-a	117	MSDDCMYDQL TRMFICSNLG GGGGVDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP

		PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK
TALL-1-12-9-a	118	MDLNCKYDEL TYKEWCQFNG GGGGVDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK
TALL-1-12-10-a	119	MFHDCKYDLL TRQMVCHGLG GGGGVDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK
TALL-1-12-11-a	120	MRNHCFWDHL LKQDICPSPG GGGGVDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK
TALL-1-12-14-a	121	MANQCWWDSL TKKNVCEFFG GGGGVDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK
TALL-1-consensus	122	MFHDCKWDLL TKQWVCHGLG GGGGVDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK
TALL-1 12-3 tandem dimer	123	MLPGCKWDLL IKQWVCDPLG SGSATGGSGS TASSGSGSAT HMLPGCKWDL LIKQWVCDPL GGGGGVDKTH TCPPCPAPEL LGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR EPQVYTLPPS RDELTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PGK
TALL-1 consensus tandem dimer	124	MFHDCKWDLL TKQWVCHGLG SGSATGGSGS TASSGSGSAT HMFHDCKWDL LTKQWVCHGL GGGGGVDKTH TCPPCPAPEL LGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR EPQVYTLPPS RDELTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PGK

Table 6. Sequences of oligonucleotides used in peptibody construction.

Oligo-nucleotide ID number	SEQ ID NO	Sequence
2517-24	71	TAT GCC GGG TAC TTG TTT CCC GTT CCC GTG GGA ATG CAC TCA CGC TGG TGG AGG CGG TGG GG
2517-25	72	TCG ACC CCA CCG CCT CCT GGA GCG TGA GTG CAT TCC CAC GGG AAG CCG AAA CAA GTA CCC GGC A
2517-26	73	TAT GTG GGG TGC TTG TTG GCC GTT CCC GTG GGA ATG TTT CAA AGA AGG TGG AGG CGG TGG GG
2517-27	74	TCG ACC CCA CCG CCT CCA CCT TCT TTG AAA CAT TCC CACGGG AAC GGC CAA CAAGCA CCC CAC A
2517-28	75	TAT GGT TCC GTT CTG TGA CCT GCT GAC TAA ACA CTG TTT CGA AGC TGG TGG AGG CGG TGG GG
2517-29	76	TCG ACC CCA CCG CCT CCA CCA GCT TCG AAA CAG TGT TTA GTC AGC AGG TCA CAGAAC GGA ACC A
2517-30	77	TAT GGG TTC TCG TTG TAA ATA CAA ATG GGA CGT TCT GAC TAA ACA GTG TTT CCA CCA CGG TGG AGG CGG TGG GG
2517-31	78	TCG ACC CCA CCG CCT CCA CCG TGG TGG AAA CAC TGT TTA GTC AGA ACG TCC CAT TTG TAT TTA CAA CGA GAA CCC A
2517-32	79	TAT GCT GCC GGG TTG TAA ATG GGA CCT GCT GAT CAA ACA GTG GGT TTG TGA CCC GCT GGG TGG AGG CGG TGG GG
2517-33	80	TCG ACC CCA CCG CCT CCA CCC AGC GGG TCA CAA ACC CAC TGT TTG ATC AGC AGG TCC CAT TTA CAA CCC GGC AGC A
2517-34	81	TAT GTC TGC TGA CTG TTA CTT CGA CAT CCT GAC TAA ATC TGA CGT TTG TAC TTC TTC TGG TGG AGG CGG TGG GG
2517-35	82	TCG ACC CCA CCG CCT CCA CCA GAA GAA GTA CAA ACG TCA GAT TTA GTC AGG ATG TCG AAG TAA CAG TCA GCA GAC A
2517-36	83	TAT GTC TGA CGA CTG TAT GTA CGA CCA GCT GAC TCG TAT GTT CAT CTG TTC TAA CCT GGG TGG AGG CGG TGG GG
2517-37	84	TCG ACC CCA CCG CCT CCA CCC AGG TTA GAA CAG ATG AAC ATA CGA GTC AGC TGG TCG TAC ATA CAG TCG TCA GAC A
2521-92	85	TAT GGA CCT GAA CTG TAA ATA CGA CGA ACT GAC TTA CAA AGA ATG GTG TCA GTT CAA CGG TGG AGG CGG TGG GG
25221-93	86	TCG ACC CCA CCG CCT CCA CCG TTG AAC TGA CAC CAT TCT TTG TAA GTC AGTTCG TCG TAT TTA CAG TTC AGG TCC A
2521-94	87	TAT GTT CCA CGA CTG TAA ATA CGA CCT GCT GAC TCG TCA GAT GGT TTG TCA CGG TCT GGG TGG AGG CGG TGG GG
2521-95	88	TCG ACC CCA CCG CCT CCA CCC AGA CCG TGA CAA ACC ATC TGA CGA GTC AGC AGG TCG TAT TTA CAG TCG TGG AAC A
2521-96	89	TAT GCG TAA CCA CTG TTT CTG GGA CCA CCT GCT GAA ACA

		GGA CAT CTG TCC GTC TCC GGG TGG AGG CGG TGG GG
2521-97	90	TCG ACC CCA CCG CCT CCA CCC GGA GAC GGA CAG ATG TCC TGT TTC AGC AGG TGG TCC CAG AAA CAG TGG TTA CGC A
2521-98	91	TAT GGC TAA CCA GTG TTG GTG GGA CTC TCT GCT GAA AAA AAA CGT TTG TGA ATT CTT CGG TGG AGG CGG TGG GG
2521-99	92	TCG ACC CCA CCG CCT CCA CCG AAG AAT TCA CAA ACG TTT TTT TTC AGC AGA GAG TCC CAC CAA CAC TGG TTA GCC A
2551-48	93	TAT GTT CCA CGA CTG CAA ATG GGA CCT GCT GAC CAA ACA GTG GGT TTG CCA CGG TCT GGG TGG AGG CGG TGG GG
2551-49	94	TCG ACC CCA CCG CCT CCA CCC AGA CCG TGG CAA ACC CAC TGT TTG GTC AGC AGG TCC CAT TTG CAG TCG TGG AAC A

pAMG21-RANK-Fc vector

pAMG21. The expression plasmid pAMG21 (ATCC accession no. 98113) can be derived from the Amgen expression vector pCFM1656 (ATCC #69576) which in turn be derived from the Amgen expression vector system described in US Patent No. 4,710,473. The pCFM1656 plasmid can be derived from the described pCFM836 plasmid (U.S. Patent No. 4,710,473) by:

- destroying the two endogenous NdeI restriction sites by end filling with T4 polymerase enzyme followed by blunt end ligation;
- replacing the DNA sequence between the unique AatII and ClaI restriction sites containing the synthetic P_L promoter with a similar fragment obtained from pCFM636 (patent No. 4,710,473) containing the P_L promoter (see SEQ ID NO: 95 below); and
- substituting the small DNA sequence between the unique ClaI and KpnI restriction sites with the oligonucleotide having the sequence of SEQ ID NO: 96.

SEQ ID NO: 95:

```
AatII
5'  CTAATTCCGCTCTCACCTACCAAACAATGCCCCCCTGCAAAAAATAAATTCATAT-
3'  TGCAGATTAAGGCGAGAGTGGATGGTTTGTTACGGGGGGACGTTTTTTATTTAAGTATA-

    -AAAAAACATACAGATAACCATCTGCGGTGATAAATTATCTCTGGCGGTGTTGACATAAA-
    -TTTTTTGTATGTCTATTGGTAGACGCCACTATTTAATAGAGACCGCCACAACTGTATTT-

    -TACCACTGGCGGTGATACTGAGCACAT 3'
    -ATGGTGACCGCCACTATGACTCGTGTAGC 5'
                                ClaI
```

SEQ ID NO: 96:

5' CGATTTGATTCTAGAAGGAGGAATAACATATGGTTAACGCGTTGGAATTCGGTAC 3'
3' TAAACTAAGATCTTCCTCCTTATTGTATACCAATTGCGCAACCTTAAGC 5'
ClaI KpnI

The expression plasmid pAMG21 can then be derived from pCFM1656 by making a series of site-directed base changes by PCR overlapping oligonucleotide mutagenesis and DNA sequence substitutions. Starting with the BglII site (plasmid bp # 180) immediately 5' to the plasmid replication promoter P_{copB} and proceeding toward the plasmid replication genes, the base pair changes are as shown in Table 7 below.

Table 7—Base pair changes resulting in pAMG21

pAMG21 bp #	bp in pCFM1656	bp changed to in pAMG21
# 204	T/A	C/G
# 428	A/T	G/C
# 509	G/C	A/T
# 617	- -	insert two G/C bp
# 679	G/C	T/A
# 980	T/A	C/G
# 994	G/C	A/T
# 1004	A/T	C/G
# 1007	C/G	T/A
# 1028	A/T	T/A
# 1047	C/G	T/A
# 1178	G/C	T/A
# 1466	G/C	T/A
# 2028	G/C	bp deletion
# 2187	C/G	T/A
# 2480	A/T	T/A
# 2499-2502	AGTG TCAC	GTCA CAGT
# 2642	TCCGAGC AGGCTCG	7 bp deletion
# 3435	G/C	A/T
# 3446	G/C	A/T
# 3643	A/T	T/A

The DNA sequence between the unique AatII (position #4364 in pCFM1656) and SacII (position #4585 in pCFM1656) restriction sites is substituted with the DNA sequence below (SEQ ID NO: 97):.

```
     [AatII sticky end]                5'     GCGTAACGTATGCATGGTCTCC-
     (position #4358 in pAMG21)        3' TGCACGCATTGCATACGTACCAGAGG-

     -CCATGCGAGAGTAGGGAACTGCCAGGCATCAAATAAAACGAAAGGCTCAGTCGAAAGACT-
5    -GGTACGCTCTCATCCCTTGACGGTCCGTAGTTTATTTTGCTTTCCGAGTCAGCTTTCTGA-

     -GGGCCTTTCGTTTTATCTGTTGTTTGTCGGTGAACGCTCTCCTGAGTAGGACAAATCCGC-
     -CCCGGAAAGCAAAATAGACAACAAACAGCCACTTGCGAGAGGACTCATCCTGTTTAGGCG-

10   -CGGGAGCGGATTTGAACGTTGCGAAGCAACGGCCCGGAGGGTGGCGGGCAGGACGCCCGC-
     -GCCCTCGCCTAAACTTGCAACGCTTCGTTGCCGGGCCTCCCACCGCCCGTCCTGCGGGCG-

     -CATAAACTGCCAGGCATCAAATTAAGCAGAAGGCCATCCTGACGGATGGCCTTTTTGCGT-
     -GTATTTGACGGTCCGTAGTTTAATTCGTCTTCCGGTAGGACTGCCTACCGGAAAAACGCA-
15
                                                          AatII
     -TTCTACAAACTCTTTTGTTTATTTTTCTAAATACATTCAAATATGGACGTCGTACTTAAC-
     -AAGATGTTTGAGAAAACAAATAAAAAGATTTATGTAAGTTTATACCTGCAGCATGAATTG-

20   -TTTTAAAGTATGGGCAATCAATTGCTCCTGTTAAAATTGCTTTAGAAATACTTTGGCAGC-
     -AAAATTTCATACCCGTTAGTTAACGAGGACAATTTTAACGAAATCTTTATGAAACCGTCG-

     -GGTTTGTTGTATTGAGTTTCATTTGCGCATTGGTTAAATGGAAAGTGACCGTGCGCTTAC-
     -CCAAACAACATAACTCAAAGTAAACGCGTAACCAATTTACCTTTCACTGGCACGCGAATG-
25
     -TACAGCCTAATATTTTTGAAATATCCCAAGAGCTTTTTCCTTCGCATGCCCACGCTAAAC-
     -ATGTCGGATTATAAAAACTTTATAGGGTTCTCGAAAAAGGAAGCGTACGGGTGCGATTTG-

     -ATTCTTTTTCTCTTTTGGTTAAATCGTTGTTTGATTTATTATTTGCTATATTTATTTTTC-
30   -TAAGAAAAAGAGAAAACCAATTTAGCAACAAACTAAATAATAAACGATATAAATAAAAAG-

     -GATAATTATCAACTAGAGAAGGAACAATTAATGGTATGTTCATACACGCATGTAAAAATA-
     -CTATTAATAGTTGATCTCTTCCTTGTTAATTACCATACAAGTATGTGCGTACATTTTTAT-

35   -AACTATCTATATAGTTGTCTTTCTCTGAATGTGCAAAACTAAGCATTCCGAAGCCATTAT-
     -TTGATAGATATATCAACAGAAAGAGACTTACACGTTTTGATTCGTAAGGCTTCGGTAATA-

     -TAGCAGTATGAATAGGGAAACTAAACCCAGTGATAAGACCTGATGATTTCGCTTCTTTAA-
     -ATCGTCATACTTATCCCTTTGATTTGGGTCACTATTCTGGACTACTAAAGCGAAGAAATT-
40
     -TTACATTTGGAGATTTTTTATTTACAGCATTGTTTTCAAATATATTCCAATTAATCGGTG-
     -AATGTAAACCTCTAAAAAATAAATGTCGTAACAAAAGTTTATATAAGGTTAATTAGCCAC-

     -AATGATTGGAGTTAGAATAATCTACTATAGGATCATATTTTATTAAATTAGCGTCATCAT-
45   -TTACTAACCTCAATCTTATTAGATGATATCCTAGTATAAAATAATTTAATCGCAGTAGTA-

     -AATATTGCCTCCATTTTTTAGGGTAATTATCCAGAATTGAAATATCAGATTTAACCATAG-
     -TTATAACGGAGGTAAAAAATCCCATTAATAGGTCTTAACTTTATAGTCTAAATTGGTATC-

50   -AATGAGGATAAATGATCGCGAGTAAATAATATTCACAATGTACCATTTTAGTCATATCAG-
     -TTACTCCTATTTACTAGCGCTCATTTATTATAAGTGTTACATGGTAAAATCAGTATAGTC-

     -ATAAGCATTGATTAATATCATTATTGCTTCTACAGGCTTTAATTTTATTAATTATTCTGT-
     -TATTCGTAACTAATTATAGTAATAACGAAGATGTCCGAAATTAAAATAATTAATAAGACA-
55
     -AAGTGTCGTCGGCATTTATGTCTTTCATACCCATCTCTTTATCCTTACCTATTGTTTGTC-
     -TTCACAGCAGCCGTAAATACAGAAAGTATGGGTAGAGAAATAGGAATGGATAACAAACAG-

     -GCAAGTTTTGCGTGTTATATATCATTAAAACGGTAATAGATTGACATTTGATTCTAATAA-
60   -CGTTCAAAACGCACAATATATAGTAATTTTGCCATTATCTAACTGTAAACTAAGATTATT-

     -ATTGGATTTTTGTCACACTATTATATCGCTTGAAATACAATTGTTTAACATAAGTACCTG-
     -TAACCTAAAAACAGTGTGATAATATAGCGAACTTTATGTTAACAAATTGTATTCATGGAC-
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-TAGGATCGTACAGGTTTACGCAAGAAAATGGTTTGTTATAGTCGATTAATCGATTTGATT-
-ATCCTAGCATGTCCAAATGCGTTCTTTTACCAAACAATATCAGCTAATTAGCTAAACTAA-

-CTAGATTTGTTTTAACTAATTAAAGGAGGAATAACATATGGTTAACGCGTTGGAATTCGA-
-GATCTAAACAAAATTGATTAATTTCCTCCTTATTGTATACCAATTGCGCAACCTTAAGCT-

                                                      SacII
-GCTCACTAGTGTCGACCTGCAGGGTACCATGGAAGCTTACTCGAGGATCCGCGGAAAGAA-
-CGAGTGATCACAGCTGGACGTCCCATGGTACCTTCGAATGAGCTCCTAGGCGCCTTTCTT-

-GAAGAAGAAGAAGAAAGCCCGAAAGGAAGCTGAGTTGGCTGCTGCCACCGCTGAGCAATA-
-CTTCTTCTTCTTCTTTCGGGCTTTCCTTCGACTCAACCGACGACGGTGGCGACTCGTTAT-

-ACTAGCATAACCCCTTGGGGCCTCTAAACGGGTCTTGAGGGGTTTTTTGCTGAAAGGAGG-
-TGATCGTATTGGGGAACCCCGGAGATTTGCCCAGAACTCCCCAAAAAACGACTTTCCTCC-

-AACCGCTCTTCACGCTCTTCACGC 3'          [SacII sticky end]
-TTGGCGAGAAGTGCGAGAAGTG   5'       (position #5904 in pAMG21)
```

During the ligation of the sticky ends of this substitution DNA sequence, the outside AatII and SacII sites are destroyed. There are unique AatII and SacII sites in the substituted DNA.

A gene encoding human RANK fused to the N-terminus of Fc was ligated into pAMG21 as an NdeI to BamHI fragment to generate Amgen Strain #4125. This construct was modified to insert a valine codon at the junction of RANK and Fc. The adjacent valine and aspartate codons create a unique SalI site. This allows for the fusion of peptides at the N-terminus of Fc3 between the unique NdeI and SalI sites. The RANK sequence is deleted upon insertion of a new NdeI-SalI fragment. The sequence of the vector is given in Figure 5A through 5M.

GM221 (Amgen #2596). The Amgen host strain #2596 is an E. coli K-12 strain derived from Amgen strain #393, which is a derivative of E. coli W1485, obtained from the E. coli Genetic Stock Center, Yale University, New Haven, Connecticut (CGSC strain 6159). It has been modified to contain both the temperature sensitive lambda repressor cI857s7 in the early ebg region and the $lacI^Q$ repressor in the late ebg region (68 minutes). The presence of these two repressor genes allows the use of this host with a variety of expression systems, however both of these repressors are irrelevant to the expression from $luxP_R$. The untransformed host has no antibiotic resistances.

The ribosome binding site of the cI857s7 gene has been modified to include an enhanced RBS. It has been inserted into the ebg operon between

nucleotide position 1170 and 1411 as numbered in Genbank accession number M64441Gb_Ba with deletion of the intervening ebg sequence. The sequence of the insert is shown below with lower case letters representing the ebg sequences flanking the insert shown below (SEQ ID NO: 98):

ttattttcgtGCGGCCGCACCATTATCACCGCCAGAGGTAAACTAGTCAACACGCACGGTGTTAGATAT
TTATCCCTTGCGGTGATAGATTGAGCACATCGATTTGATTCTAGAAGGAGGGATAATATATGAG
CACAAAAAAGAAACCATTAACACAAGAGCAGCTTGAGGACGCACGTCGCCTTAAAGCAATTTA
TGAAAAAAAGAAAAATGAACTTGGCTTATCCCAGGAATCTGTCGCAGACAAGATGGGGATGGG
GCAGTCAGGCGTTGGTGCTTTATTTAATGGCATCAATGCATTAAATGCTTATAACGCCGCATTGC
TTACAAAAATTCTCAAAGTTAGCGTTGAAGAATTTAGCCCTTCAATCGCCAGAGAATCTACGAG
ATGTATGAAGCGGTTAGTATGCAGCCGTCACTTAGAAGTGAGTATGAGTACCCTGTTTTTTCTCA
TGTTCAGGCAGGGATGTTCTCACCTAAGCTTAGAACCTTTACCAAAGGTGATGCGGAGAGATGG
GTAAGCACAACCAAAAAAGCCAGTGATTCTGCATTCTGGCTTGAGGTTGAAGGTAATTCCATGA
CCGCACCAACAGGCTCCAAGCCAAGCTTTCCTGACGGAATGTTAATTCTCGTTGACCCTGAGCA
GGCTGTTGAGCCAGGTGATTTCTGCATAGCCAGACTTGGGGGTGATGAGTTTACCTTCAAGAAA
CTGATCAGGGATAGCGGTCAGGTGTTTTTACAACCACTAAACCCACAGTACCCAATGATCCCAT
GCAATGAGAGTTGTTCCGTTGTGGGGAAAGTTATCGCTAGTCAGTGGCCTGAAGAGACGTTTGG
CTGATAGACTAGTGGATCCACTAGTgtttctgccc

The construct was delivered to the chromosome using a recombinant phage called MMebg-cI857s7enhanced RBS #4 into F'tet/393. After recombination and resolution only the chromosomal insert described above remains in the cell. It was renamed F'tet/GM101. F'tet/GM101 was then modified by the delivery of a $lacI^Q$ construct into the ebg operon between nucleotide position 2493 and 2937 as numbered in the Genbank accession number M64441Gb_Ba with the deletion of the intervening ebg sequence. The sequence of the insert is shown below with the lower case letters representing the ebg sequences flanking the insert (SEQ ID NO: 99) shown below:

ggcggaaaccGACGTCCATCGAATGGTGCAAAACCTTTCGCGGTATGGCATGATAGCGCCCGGAAGA
GAGTCAATTCAGGGTGGTGAATGTGAAACCAGTAACGTTATACGATGTCGCAGAGTATGCCGGT
GTCTCTTATCAGACCGTTTCCCGCGTGGTGAACCAGGCCAGCCACGTTTCTGCGAAAACGCGGG
AAAAAGTCGAAGCGGCGATGGCGGAGCTGAATTACATTCCCAACCGCGTGGCACAACAACTGG
CGGGCAAACAGTCGCTCCTGATTGGCGTTGCCACCTCCAGTCTGGCCCTGCACGCGCCGTCGCA
AATTGTCGCGGCGATTAAATCTCGCGCCGATCAACTGGGTGCCAGCGTGGTGGTGTCGATGGTA
GAACGAAGCGGCGTCGAAGCCTGTAAAGCGGCGGTGCACAATCTTCTCGCGCAACGCGTCAGTG
GGCTGATCATTAACTATCCGCTGGATGACCAGGATGCCATTGCTGTGGAAGCTGCCTGCACTAA
TGTTCCGGCGTTATTTCTTGATGTCTCTGACCAGACACCCATCAACAGTATTATTTTCTCCCATGA
AGACGGTACGCGACTGGGCGTGGAGCATCTGGTCGCATTGGGTCACCAGCAAATCGCGCTGTTA
GCGGGCCCATTAAGTTCTGTCTCGGCGCGTCTGCGTCTGGCTGGCTGGCATAAATATCTCACTCG
CAATCAAATTCAGCCGATAGCGGAACGGGAAGGCGACTGGAGTGCCATGTCCGGTTTTCAACAA
ACCATGCAAATGCTGAATGAGGGCATCGTTCCCACTGCGATGCTGGTTGCCAACGATCAGATGG
CGCTGGGCGCAATGCGCGCCATTACCGAGTCCGGGCTGCGCGTTGGTGCGGATATCTCGGTAGT
GGGATACGACGATACCGAAGACAGCTCATGTTATATCCCGCCGTTAACCACCATCAAACAGGAT
TTTCGCCTGCTGGGGCAAACCAGCGTGGACCGCTTGCTGCAACTCTCTCAGGGCCAGGCGGTGA

AGGGCAATCAGCTGTTGCCCGTCTCACTGGTGAAAAGAAAAACCACCCTGGCGCCCAATACGCA
AACCGCCTCTCCCCGCGCGTTGGCCGATTCATTAATGCAGCTGGCACGACAGGTTTCCCGACTGG
AAAGCGGACAGTAAGGTACCATAGGATCCaggcacagga

The construct was delivered to the chromosome using a recombinant phage called AGebg-LacIQ#5 into F'tet/GM101. After recombination and resolution only the chromosomal insert described above remains in the cell. It was renamed F'tet/GM221. The F'tet episome was cured from the strain using acridine orange at a concentration of 25 μg/ml in LB. The cured strain was identified as tetracyline sensitive and was stored as GM221.

Expression in E. coli. Cultures of each of the pAMG21-Fc-fusion constructs in E. coli GM221 were grown at 37 °C in Luria Broth medium. Induction of gene product expression from the luxPR promoter was achieved following the addition of the synthetic autoinducer N-(3-oxohexanoyl)-DL-homoserine lactone to the culture media to a final concentration of 20 ng/ml. Cultures were incubated at 37 °C for a further 3 hours. After 3 hours, the bacterial cultures were examined by microscopy for the presence of inclusion bodies and were then collected by centrifugation. Refractile inclusion bodies were observed in induced cultures indicating that the Fc-fusions were most likely produced in the insoluble fraction in E. coli. Cell pellets were lysed directly by resuspension in Laemmli sample buffer containing 10% β-mercaptoethanol and were analyzed by SDS-PAGE. In each case, an intense Coomassie-stained band of the appropriate molecular weight was observed on an SDS-PAGE gel.

EXAMPLE 3

TALL-1 peptibody inhibits TALL-1 mediated B cell proliferation

Mouse B lymphocytes were isolated from C57BL/6 spleens by negative selection. (MACS CD43 (Ly-48) Microbeads, Miltenyi Biotech, Auburn, CA). Purified (10^5) B cells were cultured in MEM, 10% heat inactivated FCS, $5x10^{-5}$M 2-mercaptoethanol, 100 U/ml penicillin, 100 μg/ml streptomycin) in triplicate in 96-well flat bottom tissue culture plates with 10 ng/ml TALL-1 protein and 2 μg/ml of Goat $F(ab')_2$ anti-mouse IgM (Jackson ImmunoResearch Laboratory,

West Grove, Pennsylvania) with the indicated amount of recombinant TALL-1 peptibody for a period of 4 days at 37 °C, 5%CO_2. Proliferation was measured by the uptake of radioactive ^{3}[H] thymidine after an 18-hour incubation period.

EXAMPLE 4

TALL-1 peptibody blocks TALL-1 binding to its receptors

Reacti-Gel 6x (Pierce) were pre-coated with human AGP3 (also known as TALL-1, Khare et al., Proc. Natl. Acad. Sci. 97:3370-3375, 2000) and blocked with BSA. 100 pM and 40 pM of AGP3 peptibody samples were incubated with indicated various concentrations of human AGP3 at room temperature for 8 hours before run through the human AGP3-coated beads. The amount of the bead-bound peptibody was quantified by fluorescent (Cy5) labeled goat anti-human-Fc antibody (Jackson Immuno Research). The binding signal is proportional to the concentration of free peptibody at binding equilibrium. Dissociation equilibrium constant (K_D) was obtained from nonlinear regression of the competition curves using a dual-curve one-site homogeneous binding model (KinEx™ software). K_D is about 4 pM for AGP3 peptibody (SEQ ID NO: 123) binding with human AGP3 (Figure 10).

To determine if this AGP3 peptibody can neutralize murine AGP3 binding as well as human AGP3, a BIAcore neutralizing assay was utilized. All experiments were performed on a BIAcore 3000 at room temperature. Human TACI-Fc protein (Xia et al, J. Exp. Med. 192, 137-144, 2000) was immobilized to a B1 chip using 10 mM Acetate pH 4.0 to a level of 2900RU. A blank flow cell was used as a background control. Using a running buffer of PBS (without calcium or magnesium) containing 0.005% P20, 1 nM recombinant human AGP3 (in running buffer plus, 0.1 mg/ml BSA) was incubated without and with indicated various amount of AGP3 peptibody (x axis) before injected over the surface of the receptor. Regeneration was performed using 8 mM glycine pH 1.5 for 1 minute, 25 mM 3-[cyclohexylamino]-1-propanesulfonic acid (CAPS) pH 10.5, 1 M NaCl for 1 minute. For determination of murine AGP3 binding, human his-tagged

TACI was immobilized to 1000 RU in the above buffer. 5 nM recombinant murine AGP3 (in running buffer plus, 0.1 mg/ml BSA) was incubated without and with the various amounts indicated in Figure 11 of AGP3 peptibody (x axis) before injected over the surface of the receptor. Regeneration was performed with 10 mM HCl pH2, twice for 30 seconds. Relative binding of both human and murine AGP3 at presence vs absence of AGP3 peptibody (SEQ ID NO: 123) was measured (y axis). Relative binding response was determined as (RU-RU blank/ RUo-RU blank). The AGP3 peptibody (SEQ ID NO: 123) inhibited both human and murine AGP3 binding to its receptor TACI (Figures 11A and 11B).

To examine if this AGP3 peptibody blocks AGP3 binding to all three receptors (TACI, BCMA and BAFFR), recombinant soluble receptor TACI, BCMA and BAFFR proteins were immobilized to CM5 chip. Using 10 mM acetate, pH4, human TACI-Fc was immobilized to 6300 RU, human BCMA-Fc to 5000 RU, and BAFFR-Fc to 6000 RU. 1 nM of recombinant human AGP3 (in running buffer containing 0.1 mg/ml BSA and 0.1 mg/ml Heparin) or 1 nM recombinant APRIL protein (Yu, et al., Nat. Immunol., 1:252-256, 2000) were incubated with indicated amount of AGP3 peptibody before injection over each receptor surface. Regeneration for the AGP3 experiment was done with 8 mM glycine, pH 1.5, for 1 minute, followed by 25 mM CAPS, pH 10.5, 1M NaCl for 1 minute. Regeneration for the APRIL experiment was performed with 8 mM glycine, pH 2, for one minute, followed by 25 mM CAPS, pH 10.5, 1 M NaCl for one minute. Relative binding of AGP3 or APRIL was measured. AGP3 peptibody (SEQ ID NO: 123) blocked AGP3 binding to all three receptors (Figure 12A). AGP3 peptibody didn't affect APRIL binding to the receptors (Figure 12B).

EXAMPLE 5

AGP3 peptibody blocks AGP3 mediated B cell proliferation

Mouse B lymphocytes were isolated from C57BL/6 spleens by negative selection. (MACS CD43 (Ly-48) Microbeads, Miltenyi Biotech, Auburn, CA).

Purified (10^5) B cells were cultured in minimal essential medium (MEM), 10% heat inactivated fetal calf serum (FCS), $5x10^{-5}$ M 2-mercaptoethanol, 100 U/ml penicillin, 100 µg/ml streptomycin) in triplicate in 96-well flat bottom tissue culture plates with 10 ng/ml AGP3 (TALL-1) protein and 2 µg/ml of Goat $F(ab')_2$ anti-mouse IgM (Jackson ImmunoResearch Laboratory, West Grove, Pennsylvania) with the indicated amount of recombinant AGP3 peptibody (SEQ ID NO: 123) for a period of 4 days at 37 °C, 5% CO_2. Proliferation was measured by the uptake of radioactive ^{3}[H] thymidine after an 18-hour incubation period.

EXAMPLE 6

AGP3 peptibody on AGP3-stimulated Ig production in mice

Mice (Balb/c females of 9-14 weeks of age and 19-21 g of weight) were purchased from Charles River Laboratories, Wilmington, MA. Mice (n = 10) were treated i.p. with 1 mg/Kg of human AGP3 once a day for five consecutive days followed by 5 mg/Kg or 0.5 mg/Kg of AGP3 peptibody (SEQ ID NO: 123) or by saline or by 5 mg/Kg of human Fc. Other mice were left untreated. Mice were sacrificed on the sixth day to measure serum IgM and IgA, which were measured by ELISA. Briefly, plates were coated with capture antibodies specific for IgM or IgA (Southern Biotechnology Associates, Birmingham, AL), blocked, and added with dilutions of standard (IgM from Calbiochem, San Diego, CA and IgA from Southern Biotechnology Associates) or test samples. Captured Ig were revealed using biotinylated antibodies specific for IgM or IgA (Southern Biotechnology Associates), neutravidin-conjugated peroxidase (Pierce, Rockford, IL), and tetramethylbenzidine (TMB) microwell peroxidase substrate (KPL, Gaithersburg, MD). Optical densities were quantitated in a Thermomax ELISA reader (Molecular Devices, Menlo Park, CA).

Human AGP3-stimulated increase in serum levels of IgM and IgA was blocked by 5 mg/Kg of the anti-AGP3 peptibody (SEQ ID NO: 123) and not by 0.5 mg/Kg (Figures 14A and 14B).

EXAMPLE 7

AGP3 peptibody reduced spleen B cell number in mice

Mice (as above, n = 7) were treated i.p. for seven consecutive days with 5 mg/Kg or 1.5 mg/Kg or 0.5 mg/Kg of AGP3 peptibody (SEQ ID NO: 123) or with saline or with 5 mg/Kg of human Fc. Mice were sacrificed on the eighth day to count spleen B cell number. Spleens were collected in saline and gently disrupted by manual homogenization to yield a cell suspension. The total cell number was obtained with a H1E counter (Technicon, Tarrytown, NY). Percentages of B cells were derived by immunofluorescence double staining and flow cytometry using fluorescein isothiocyanate (FITC)-conjugated and phycoerythrin (PE)-conjugated Ab against CD3 and B220, respectively (PharMingen, San Diego, CA) and a FACScan analyser (Becton and Dickinson, Mountain View, CA). B cells were identified for being CD3-B220+. At all doses, the AGP3 peptibody (SEQ ID NO: 123) decreased spleen B cell number in a dose-response fashion (Figure 14) (SEQ ID NO: 123).

EXAMPLE 8

AGP3 peptibody reduced arthritis severity in mouse CIA model

Eight to 12 week old DBA/1 mice (obtained from Jackson Laboratories, Bar Harbor, ME) were immunized with bovine collagen type II (bCII) (purchased from University of Utah), emulsified in complete Freunds adjuvant (Difco) intradermally at the base of tail. Each injection was 100 µl containing 100 µg of bCII. Mice were boosted 3 weeks after the initial immunization with bCII emulsified in incomplete Freunds adjuvant. Treatment was begun from the day of booster immunization for 4 weeks. Mice were examined for the development of arthritis. As described before (Khare et al., J. Immunol. 155: 3653-9, 1995), all four paws were individually scored from 0-3. Therefore arthritis severity could vary from 0 to 12 for each animal. AGP3 (SEQ ID NO: 123) peptibody treatment significantly reduced the severity of arthritic scores (Figure 15).

Serum samples were taken one week after final treatment (day 35) for the analysis of anti-collagen antibody level. High binding ELISA plates (Immulon, Nunc) were coated with 50 µl of 4 µg/ml solution of bovine CII in carbonate buffer and plated were kept in cold overnight in the refrigerator. Plates were washed three times with cold water. 75 µl of blocking solution made up of PBS/.05% tween 20/1% BSA was used to block non-specific binding for an hour. Samples were diluted (in blocking buffer) in dilution plates at 1:25, 1:100, 1:400, and 1:1600 and 25 µl of these samples were added to each well of the ELISA plate for a final dilution of 100, 400, 1600, and 6400 with a final volume of 100 µl/well. After incubation at room temperature for 3 hours, plates were washed three times again. 100 µl of secondary antibody diluted in blocking buffer (rat anti-mouse IgM, IgG2a, IgG2b, IgG1, IgG3-HRP) was added to each well and plates were incubated for at least 2 hours. Plates were washed four times. 100 µl of TMB solution (Sigma) was added to each well and the reaction was stopped using 50 µl of 25% sulfuric acid. Plates were read using an ELISA plate reader at 450 nm. OD was compared with a standard pool representing units/ml. AGP3 peptibody (SEQ ID NO: 123) treatment reduced serum anti-collagen II IgG1, IgG3, IgG2a, and IgG2b levels compared to PBS or Fc control treatment groups (Figure 16).

EXAMPLE 9

Treatment of AGP3 peptibody in NZB/NZW lupus mice

Five month old lupus prone NZBx NZBWF1 mice were treated i.p. 3X/week for 8 weeks with PBS or indicated doses of AGP3 peptibody or human Fc proteins. Prior to the treatment, animals were pre-screened for protein in the urine with Albustix reagents strips (Bayer AG). Mice having greater than 100 mg/dl of protein in the urine were not included in the study. Protein in the urine was evaluated monthly throughout the life of the experiment. AGP3 peptibody (SEQ ID NO: 123) treatment led to delay of proteinuria onset and improved survival (Figure 17).

AGP3 peptibody treatment reduced B cell number in mice. Balb/c mice received 7 daily intraperitoneal injections of indicated amount of AGP3 peptibody (SEQ ID NO: 123) or human Fc protein. On day 8, spleens were collected, and subject to FACS analysis for B220+ B cells as set for in Table 8.

Table 8

AGP3 Pb Reduces B Cell Number in Normal Mice

n=7	dose (1/dayx7)	spleen B cell (1x10e6)	SD	t test
saline		51.3	9.6	
Fc	5mg/Kg	45.5	7.1	
Peptibody	5mg/Kg	20.1	3.8	1.37856E-05
	1.5mg/Kg	22.6	6.9	5.10194E-05
	0.5mg/Kg	25.8	3.6	0.000111409

* * *

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto, without departing from the spirit and scope of the invention as set forth herein.

What is claimed is:

1. A TALL-1-binding composition of matter comprising an amino acid sequence Dz^2Lz^4, wherein z^2 is an amino acid residue and z^4 is T or I, and wherein the composition of matter does not comprise a fragment of TACI, BCMA, or BAFFR (SEQ ID NOS: 195, 196, and 197).
2. The composition of matter of Claim 1, wherein z^4 is T.
3. A TALL-1-binding composition of matter comprising an amino acid sequence Dz^2LI, wherein z^2 is an amino acid residue.
4. The composition of matter of Claim 1 comprising an amino acid sequence of the formula

$$a^1a^2a^3CDa^6La^8a^9a^{10}Ca^{12}a^{13}a^{14}$$

(SEQ. ID. NO: 100)

wherein:

a^1, a^2, a^3 are each independently absent or amino acid residues;

a^6 is an amino acid residue;

a^8 is T or I;

a^9 is a basic or hydrophobic residue;

a^{12} is a neutral polar residue; and

a^{13} and a^{14} are each independently absent or amino acid residues.

5. The composition of matter of Claim 4 wherein a^8 is T and a^9 is a basic residue.
6. The composition of matter of Claim 4 wherein a^9 is K and a^{12} is F.
7. The composition of matter of Claim 1 comprising an amino acid sequence of the formula

$$b^1b^2b^3Cb^5b^6Db^8Lb^{10}b^{11}b^{12}b^{13}b^{14}Cb^{16}b^{17}b^{18}$$

(SEQ. ID. NO: 104)

wherein:

b^1 and b^2 are each independently absent or amino acid residues;

b^3 is an acidic or amide residue;

b^5 is an amino acid residue;

b^6 is an aromatic residue;

b^8 is an amino acid residue;

b^{10} is T or I;

b^{11} is a basic residue;

b^{12} and b^{13} are each independently amino acid residues;

b^{14} is a neutral polar residue; and

b^{16}, b^{17}, and b^{18} are each independently absent or amino acid residues.

8. The composition of matter of Claim 7 wherein:

b^3 is D, Q, or E;

b^6 is W or Y;

b^{10} is T;

b^{11} is K or R; and

b^{14} is V or L.

9. The composition of matter of Claim 1 comprising an amino acid sequence of the formula

$$c^1c^2c^3Cc^5Dc^7L\ c^9c^{10}c^{11}c^{12}c^{13}c^{14}Cc^{16}c^{17}c^{18}$$

(SEQ. ID. NO: 105)

wherein:

c^1, c^2, and c^3 are each independently absent or amino acid residues;

c^5 is an amino acid residue;

c^7 is an amino acid residue;

c^9 is T or I;

c^{10} is a basic residue;

c^{11} and c^{12} are each independently amino acid residues;

c^{13} is a neutral polar residue;

c^{14} is an amino acid residue;

c^{16} is an amino acid residue;

c^{17} is a neutral polar residue; and

c^{18} is an amino acid residue or is absent.

10. The composition of matter of Claim 9 wherein:

c^9 is T;

c^{10} is K or R;

c^{13} is a I, L, or V; and

c^{17} is A or L.

11. The composition of matter of Claim 1 comprising an amino acid sequence of the formula

$$d^1d^2d^3Cd^5d^6d^7WDd^{10}Ld^{12}d^{13}d^{14}Cd^{15}d^{16}d^{17}$$

(SEQ. ID. NO: 106)

wherein:

d^1, d^2, and d^3 are each independently absent or amino acid residues;

d^5, d^6, and d^7 are each independently amino acid residues;

d^{10} is an amino acid residue;

d^{13} is T or I;

d^{14} is an amino acid residue; and

d^{16}, d^{17}, and d^{18} are each independently absent or amino acid residues.

12. The composition of matter of Claim 1 comprising an amino acid sequence of the formula

$$e^1e^2e^3Ce^5e^6e^7De^9L\ e^{11}Ke^{13}Ce^{15}e^{16}e^{17}e^{18}$$

(SEQ. ID. NO: 107)

wherein:

e^1, e^2, and e^3 are each independently absent or amino acid residues;

e^5, e^6, e^7, e^9, and e^{13} are each independently amino acid residues;

e^{11} is T or I; and

e^{15}, e^{16}, and e^{17} are each independently absent or amino acid residues.

13. The composition of matter of Claim 1 comprising an amino acid sequence of the formula

$f^1f^2f^3Kf^5Df^7Lf^9f^{10}Qf^{12}f^{13}f^{14}$

(SEQ ID NO: 109)

wherein:

f^1, f^2, and f^3 are absent or are amino acid residues;

f^5 is W, Y, or F;

f^7 is an amino acid residue;

f^9 is T or I;

f^{10} is K, R, or H;

f^{12} is C, a neutral polar residue, or a basic residue (W, C, or R preferred);

f^{13} is C, a neutral polar residue or is absent; and

f^{14} is any amino acid residue or is absent;

provided that only one of f^1, f^2, and f^3 may be C, and only one of f^{12}, f^{13}, and f^{14} may be C.

14. The composition of matter of Claim 13, wherein f^5 is W.

15. The composition of matter of Claim 13, wherein f^7 is L.

16. The composition of matter of Claim 13, wherein f^9 is T.

17. The composition of matter of Claim 13, wherein f^{10} is K.

18. The composition of matter of Claim 13, wherein f^{12} is C and one of f^1, f^2, and f^3 is C.

19. The composition of matter of Claim 13, wherein f^{13} is V.

20. The composition of matter of Claim 13 comprising an amino acid sequence of the formula

$f^1f^2f^3KWDf^7Lf^9KQf^{12}f^{13}f^{14}$

(SEQ ID NO: 125).

21. The composition of matter of Claim 20 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 32, 33, 58,

60, 63, 66, 67, 69, 114, 115, 122, 123, 124, 147-150, 152-177, 179, 180, and 187.

22. The composition of matter of Claim 20 comprising an amino acid sequence of the formula

LPGCKWDLLIKQWVCDPL (SEQ ID NO: 33).

23. A composition of matter comprising an amino acid sequence of the formula

$g^1g^2g^3Cg^5PFg^8Wg^{10}Cg^{11}g^{12}g^{13}$

(SEQ. ID. NO: 101)

wherein:

g^1, g^2 and g^3 are each independently absent or amino acid residues;

g^5 is a neutral polar residue;

g^8 is a neutral polar residue;

g^{10} is an acidic residue;

g^{12} and g^{13} are each independently amino acid residues; and

g^{14} is absent or is an amino acid residue.

24. The composition of matter of Claim 23 wherein:

g^2 is G;

g^5 is W;

g^8 is P;

g^{10} is E; and

g^{13} is a basic residue.

25. A composition of matter comprising an amino acid sequence of the formula

$h^1h^2h^3CWh^6h^7WGh^{10}Ch^{12}h^{13}h^{14}$

(SEQ. ID. NO: 102)

wherein:

h^1, h^2, and h^3 are each independently absent or amino acid residues;

h^6 is a hydrophobic residue;

h^7 is a hydrophobic residue;

h^{10} is an acidic or polar hydrophobic residue; and

h^{12}, h^{13}, and h^{14} are each independently absent or amino acid residues.

26. The composition of matter of Claim 25 wherein:

h^1 is G;

h^6 is A;

h^7 is a neutral polar residue; and

h^{10} is an acidic residue.

27. A composition of matter comprising an amino acid sequence of the formula

$$i^1i^2i^3Ci^5i^6i^7i^8i^9i^{10}Ci^{12}i^{13}i^{14}$$

(SEQ. ID. NO: 103)

wherein:

i^1 is absent or is an amino acid residue;

i^2 is a neutral polar residue;

i^3 is an amino acid residue;

i^5, i^6, i^7, and i^8 are each independently amino acid residues;

i^9 is an acidic residue;

i^{10} is an amino acid residue;

i^{12} and i^{13} are each independently amino acid residues; and

i^{14} is a neutral polar residue.

28. The composition of matter of Claim 27 wherein:

i^2 is W; and

i^{14} is W.

29. A TALL-1 binding composition of matter comprising an amino acid sequence of the formula PFPWE (SEQ ID NO: 110). :

30. The composition of matter of Claim 1 having the formula

$$(X^1)_a\text{-}V^1\text{-}(X^2)_b$$

and multimers thereof, wherein:

V^1 is a vehicle;

X^1 and X^2 are each independently selected from $-(L^1)_c-P^1$,

$-(L^1)_c-P^1-(L^2)_d-P^2$, $-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3$, and

$-(L^1)_c-P^1-(L^2)_d-P^2-(L^3)_e-P^3-(L^4)_f-P^4$

one or more of P^1, P^2, P^3, and P^4 each independently comprise

Dz^2Lz^4;

L^1, L^2, L^3, and L^4 are each independently linkers; and

a, b, c, d, e, and f are each independently 0 or 1, provided that at least one of a and b is 1.

31. The composition of matter of Claim 30 of the formula

$$P^1-(L^1)_c-P^2-(L^2)_d-V^1.$$

32. The composition of matter of Claim 30 of the formula

$$V^1-(L^1)_c-P^1-(L^2)_d-P^2.$$

33. The composition of matter of Claim 30, wherein V^1 is an Fc domain.

34. The composition of matter of Claim 30 wherein V^1 is an IgG Fc domain.

35. The composition of matter of Claim 30 wherein V^1 is an IgG1 Fc domain.

36. The composition of matter of Claim 30 wherein V^1 comprises the sequence of SEQ ID NO: 2.

37. The composition of matter of Claim 30 wherein one or more of P^1, P^2, P^3, and P^4 each independently comprises a sequence selected from:

$a^1a^2a^3CDa^6La^8a^9a^{10}Ca^{12}a^{13}a^{14}$ (SEQ. ID. NO: 100)

$b^1b^2b^3Cb^5b^6Db^8Lb^{10}b^{11}b^{12}b^{13}b^{14}Cb^{16}b^{17}b^{18}$ (SEQ. ID. NO: 104)

$c^1c^2c^3Cc^5Dc^7Lc^9c^{10}c^{11}c^{12}c^{13}c^{14}Cc^{16}c^{17}c^{18}$ (SEQ. ID. NO: 105)

$d^1d^2d^3Cd^5d^6d^7WDd^{10}Ld^{13}d^{14}d^{15}Cd^{16}d^{17}d^{18}$ (SEQ. ID. NO: 106)

$e^1e^2e^3Ce^5e^6e^7De^9Le^{11}Ke^{13}Ce^{15}e^{16}e^{17}e^{18}$ (SEQ. ID. NO: 107)

$f^1f^2f^3Kf^5Df^7Lf^9f^{10}Qf^{12}f^{13}f^{14}$ (SEQ. ID. NO: 109)

$g^1g^2g^3Cg^5PFg^8Wg^{10}Cg^{11}g^{12}g^{13}$ (SEQ ID NO: 101),

$h^1h^2h^3CWh^6h^7WGh^{10}Ch^{12}h^{13}h^{14}$ (SEQ ID NO: 102), and

$i^1i^2i^3Ci^5i^6i^7i^8i^9i^{10}Ci^{12}i^{13}i^{14}$ (SEQ ID NO: 103)

wherein:

a^1, a^2, a^3 are each independently absent or amino acid residues;

a^6 is an amino acid residue;

a^9 is a basic or hydrophobic residue;

a^8 is threonyl or isoleucyl;

a^{12} is a neutral polar residue;

a^{13} and a^{14} are each independently absent or amino acid residues;

b^1 and b^2 are each independently absent or amino acid residues;

b^3 is an acidic or amide residue;

b^5 is an amino acid residue;

b^6 is an aromatic residue;

b^8 is an amino acid residue;

b^{10} is T or I;

b^{11} is a basic residue;

b^{12} and b^{13} are each independently amino acid residues;

b^{14} is a neutral polar residue;

b^{16}, b^{17}, and b^{18} are each independently absent or amino acid residues;

c^1, c^2, and c^3 are each independently absent or amino acid residues;

c^5 is an amino acid residue;

c^7 is an amino acid residue;

c^9 is T or I;

c^{10} is a basic residue;

c^{11} and c^{12} are each independently amino acid residues;

c^{13} is a neutral polar residue;

c^{14} is an amino acid residue;

c^{16} is an amino acid residue;

c^{17} is a neutral polar residue; and

c^{18} is an amino acid residue or is absent;

d^1, d^2, and d^3 are each independently absent or amino acid residues;

d^5, d^6, and d^7 are each independently amino acid residues;

d^{10} is an amino acid residue;

d^{12} is T or I;

d^{13} is an amino acid residue; and

d^{15}, d^{16}, and d^{17} are each independently absent or amino acid residues;

e^1, e^2, and e^3 are each independently absent or amino acid residues;

e^5, e^6, e^7, e^9, and e^{13} are each independently amino acid residues;

e^{11} is T or I; and

e^{15}, e^{16}, and e^{17} are each independently absent or amino acid residues;

f^1, f^2, and f^3 are absent or are amino acid residues;

f^5 is W, Y, or F;

f^7 is an amino acid residue;

f^9 is T or I;

f^{10} is K, R, or H;

f^{12} is C, a neutral polar residue, or a basic residue;

f^{13} is C, a neutral polar residue or is absent; and

f^{14} is any amino acid residue or is absent;

provided that only one of f^1, f^2, and f^3 may be C, and only one of f^{12}, f^{13}, and f^{14} may be C;

g^1, g^2 and g^3 are each independently absent or amino acid residues;

g^5 is a neutral polar residue;

g^8 is a neutral polar residue;

g^{10} is an acidic residue;

g^{12} and g^{13} are each independently amino acid residues; and

g^{14} is absent or is an amino acid residue;

h^1, h^2, and h^3 are each independently absent or amino acid residues;

h^6 is a hydrophobic residue;

h^7 is a hydrophobic residue;

h^{10} is an acidic or polar hydrophobic residue; and

h^{12}, h^{13}, and h^{14} are each independently absent or amino acid residues;

i^1 is absent or is an amino acid residue;

i^2 is a neutral polar residue;

i^3 is an amino acid residue;

i^5, i^6, i^7, and i^8 are each independently amino acid residues;

i^9 is an acidic residue;

i^{10} is an amino acid residue;

i^{12} and i^{13} are each independently amino acid residues; and

i^{14} is a neutral polar residue.

38. The composition of matter of claim 37, wherein:

a^9 is a basic residue.

b^3 is D, Q, or E;

b^6 is W or Y;

b^{11} is K or R; and

b^{14} is V or L.

c^{10} is K or R;

c^{13} is a I, L, or V;

c^{17} is A or L;

f^5 is W;

f^7 is L; f^7 is K; and

f^{10} is V.

39. The composition of matter of Claim 37, wherein one or more of P^1, P^2, P^3, and P^4 each independently comprises

$f^1f^2f^3KWDf^7Lf^9KQf^{12}f^{13}f^{14}$

(SEQ ID NO: 125).

40. The composition of matter of Claim 39 of the formula

$$P^1\text{-}(L^1)_c\text{-}P^2\text{-}(L^2)_d\text{-}V^1.$$

41. The composition of matter of Claim 39 of the formula

$$V^1\text{-}(L^1)_c\text{-}P^1\text{-}(L^2)_d\text{-}P^2.$$

42. The composition of matter of Claim 39 having an amino acid sequence selected from SEQ ID NOS: 122, 123, and 124.

43. The composition of matter of Claim 40 wherein L^2 is greater than 5 amino acids.

44. The composition of matter of Claim 43 wherein L^2 is selected from

GSGSATGGSGSTASSGSGSATx^{1}x^2

(SEQ ID NO: 193)

and

GSGSATGGSGSTASSGSGSATx^{1}x^{2}GSGSATGGSGSTASSGSGSATx^{3}x^4

(SEQ ID NO: 194)

wherein x^1 and x^3 are each independently basic or hydrophobic residues and x^2 and x^4 are each independently hydrophobic residues.

45. The composition of matter of Claim 41 wherein L^2 is selected from

GSGSATGGSGSTASSGSGSATH

(SEQ ID NO: 59),

GSGSATGGSGSTASSGSGSATGM

(SEQ ID NO: 190)

GSGSATGGSGSTASSGSGSATGS

(SEQ ID NO: 191), and

GSGSATGGSGSTASSGSGSATHMGSGSATGGSGSTASSGSGSATHM

(SEQ ID NO: 192).

46. The composition of matter of Claim 28 comprising a sequence selected from Table 2 (SEQ ID NOS: 29-39, 60-70, and 126-188).

47. The composition of matter of Claim 30 comprising a sequence selected from Table 4 (SEQ ID NOS: 44-55).

48. The composition of matter of Claim 46, wherein V^1 is an Fc domain.

49. The composition of matter of Claim 46, wherein V^1 is an IgG Fc domain.

50. The composition of matter of Claim 46, wherein V^1 is an IgG1 Fc domain.

51. A DNA encoding a composition of matter of Claim 34.

52. An expression vector comprising the DNA of Claim 51.

53. A host cell comprising the expression vector of Claim 52.

54. The cell of Claim 53, wherein the cell is an E. coli cell.

55. A method of treating a B-cell mediated autoimmune disease, which comprises administering a composition of matter of Claim 1.

56. A method of treating a B-cell mediated autoimmune disease, which comprises administering a composition of matter of Claim 13.

57. A method of treating lupus, which comprises administering a composition of matter of Claim 1.

58. A method of treating lupus, which comprises administering a composition of matter of Claim 13.

59. A method of treating a B-cell mediated cancer, which comprises administering a composition of matter of Claim 1.

60. A method of treating a B-cell mediated cancer, which comprises administering a composition of matter of Claim 13.

61. A method of treating B-cell lymphoma, which comprises administering a composition of matter of Claim 1.

62. A method of treating B-cell lymphoma, which comprises administering a composition of matter of Claim 13.

FIG.1

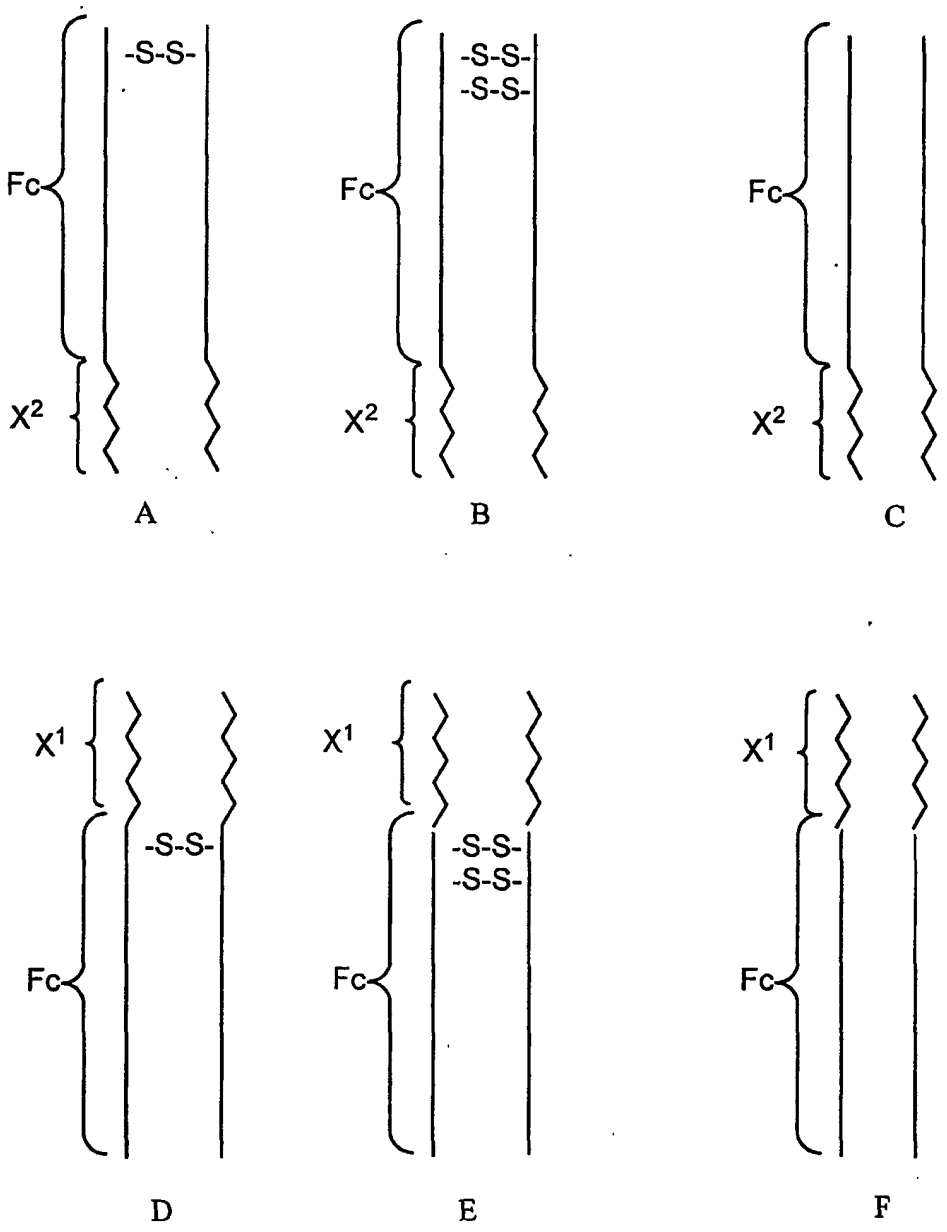


FIG. 2

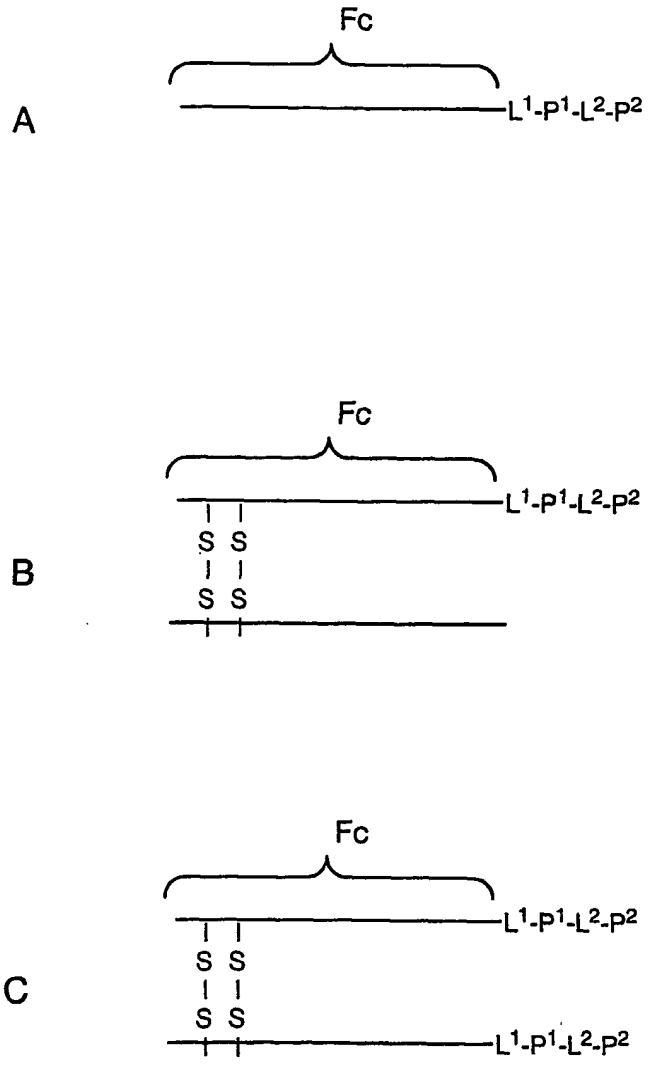


FIG. 3

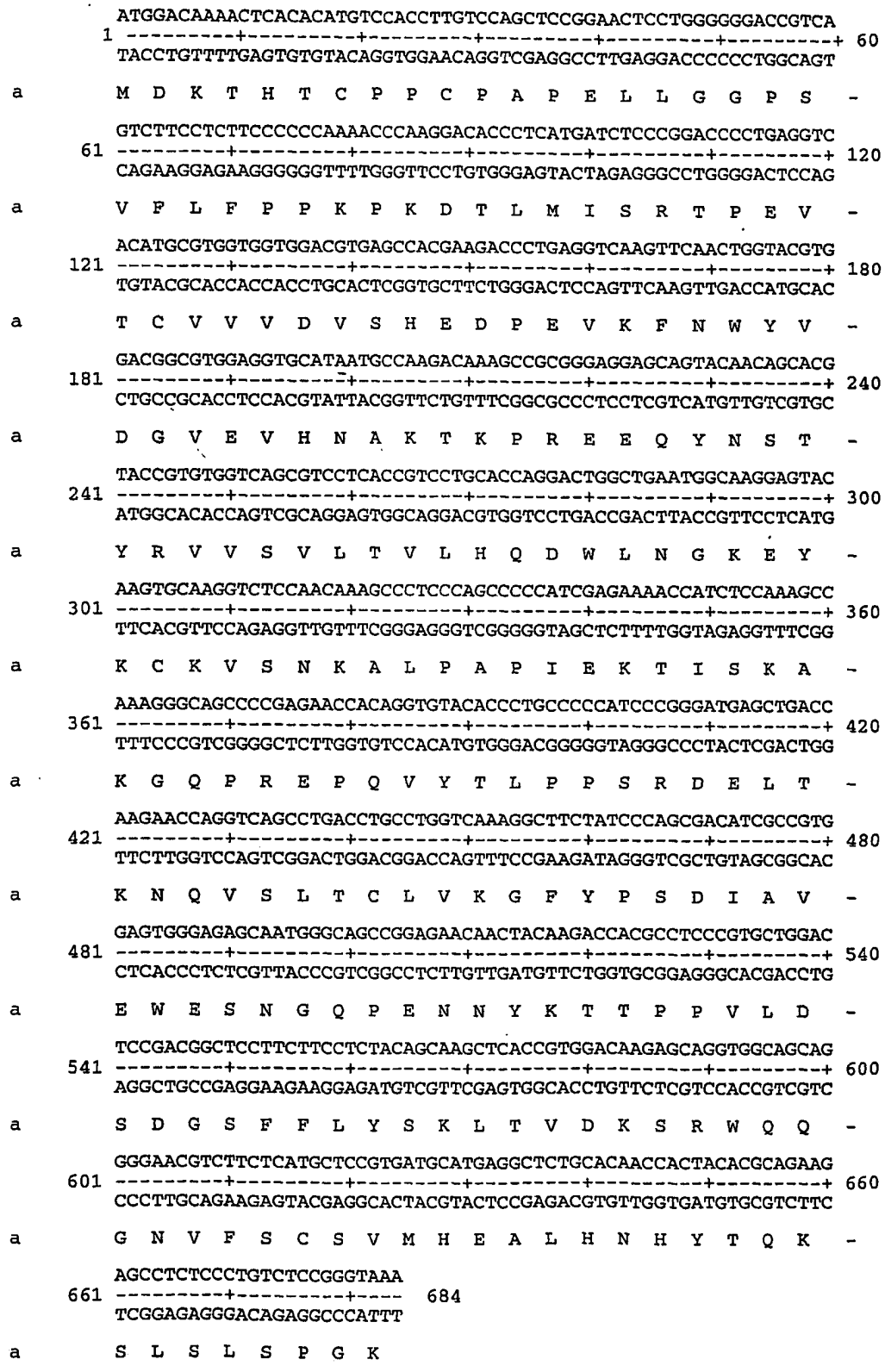

ATGGACAAAACTCACACATGTCCACCTTGTCCAGCTCCGGAACTCCTGGGGGGACCGTCA
1 ---------+---------+---------+---------+---------+---------+ 60
TACCTGTTTTGAGTGTGTACAGGTGGAACAGGTCGAGGCCTTGAGGACCCCCCTGGCAGT
a M D K T H T C P P C P A P E L L G G P S -
GTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTC
61 ---------+---------+---------+---------+---------+---------+ 120
CAGAAGGAGAAGGGGGGTTTTGGGTTCCTGTGGGAGTACTAGAGGGCCTGGGGACTCCAG
a V F L F P P K P K D T L M I S R T P E V -
ACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTG
121 ---------+---------+---------+---------+---------+---------+ 180
TGTACGCACCACCACCTGCACTCGGTGCTTCTGGGACTCCAGTTCAAGTTGACCATGCAC
a T C V V V D V S H E D P E V K F N W Y V -
GACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACG
181 ---------+---------+---------+---------+---------+---------+ 240
CTGCCGCACCTCCACGTATTACGGTTCTGTTTCGGCGCCCTCCTCGTCATGTTGTCGTGC
a D G V E V H N A K T K P R E E Q Y N S T -
TACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTAC
241 ---------+---------+---------+---------+---------+---------+ 300
ATGGCACACCAGTCGCAGGAGTGGCAGGACGTGGTCCTGACCGACTTACCGTTCCTCATG
a Y R V V S V L T V L H Q D W L N G K E Y -
AAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCC
301 ---------+---------+---------+---------+---------+---------+ 360
TTCACGTTCCAGAGGTTGTTTCGGGAGGGTCGGGGGTAGCTCTTTTGGTAGAGGTTTCGG
a K C K V S N K A L P A P I E K T I S K A -
AAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACC
361 ---------+---------+---------+---------+---------+---------+ 420
TTTCCCGTCGGGGCTCTTGGTGTCCACATGTGGGACGGGGGTAGGGCCCTACTCGACTGG
a K G Q P R E P Q V Y T L P P S R D E L T -
AAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTG
421 ---------+---------+---------+---------+---------+---------+ 480
TTCTTGGTCCAGTCGGACTGGACGGACCAGTTTCCGAAGATAGGGTCGCTGTAGCGGCAC
a K N Q V S L T C L V K G F Y P S D I A V -
GAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGAC
481 ---------+---------+---------+---------+---------+---------+ 540
CTCACCCTCTCGTTACCCGTCGGCCTCTTGTTGATGTTCTGGTGCGGAGGGCACGACCTG
a E W E S N G Q P E N N Y K T T P P V L D -
TCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAG
541 ---------+---------+---------+---------+---------+---------+ 600
AGGCTGCCGAGGAAGAAGGAGATGTCGTTCGAGTGGCACCTGTTCTCGTCCACCGTCGTC
a S D G S F F L Y S K L T V D K S R W Q Q -
GGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAG
601 ---------+---------+---------+---------+---------+---------+ 660
CCCTTGCAGAAGAGTACGAGGCACTACGTACTCCGAGACGTGTTGGTGATGTGCGTCTTC
a G N V F S C S V M H E A L H N H Y T Q K -
AGCCTCTCCCTGTCTCCGGGTAAA
661 ---------+---------+---- 684
TCGGAGAGGGACAGAGGCCCATTT
a S L S L S P G K

FIG. 4A

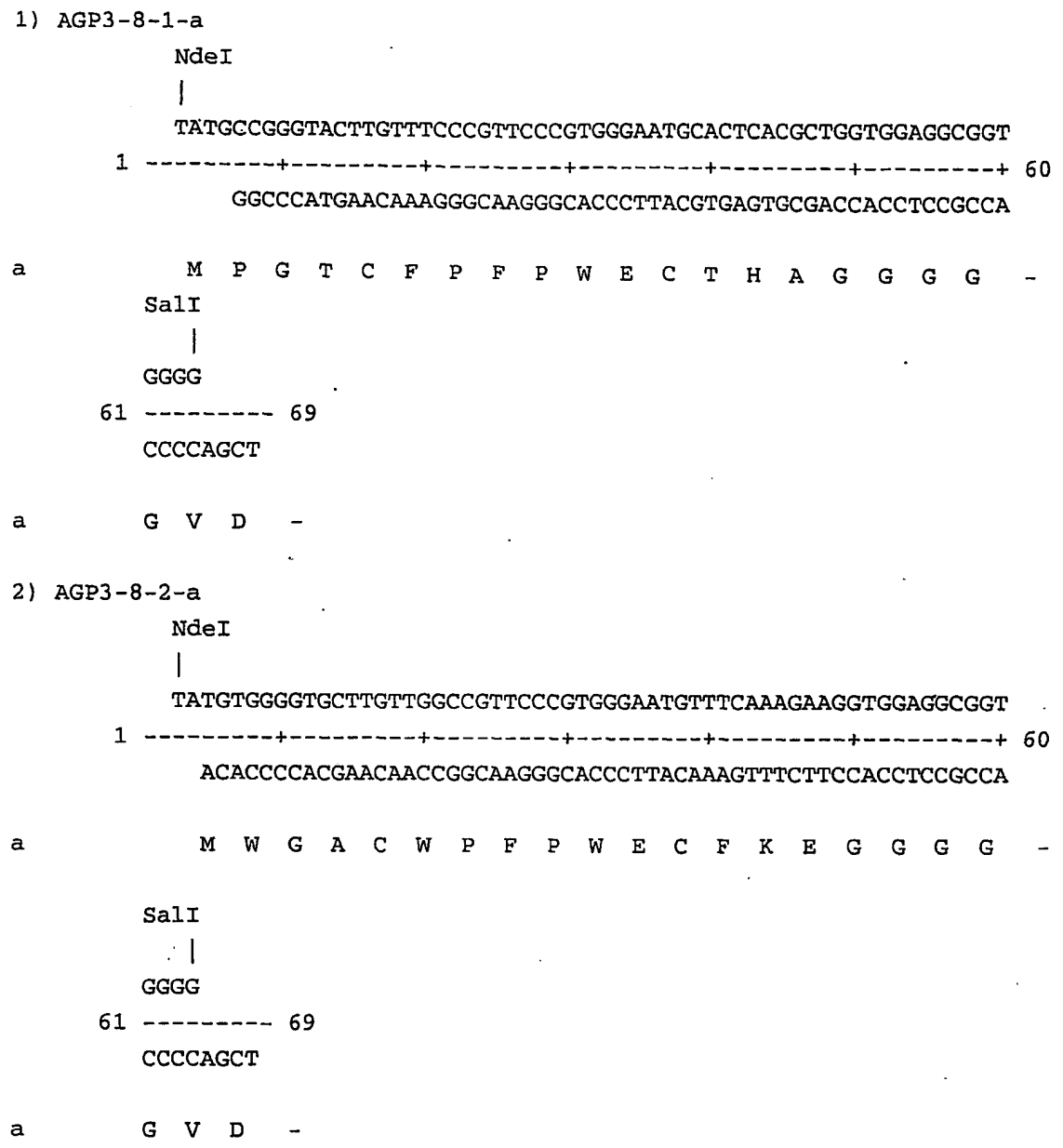

1) AGP3-8-1-a
NdeI
TATGCCGGGTACTTGTTTCCCGTTCCCGTGGGAATGCACTCACGCTGGTGGAGGCGGT
1
60
GGCCCATGAACAAAGGGCAAGGGCACCCTTACGTGAGTGCGACCACCTCCGCCA
a M P G T C F P F P W E C T H A G G G G -
SalI
GGGG
61
69
CCCCAGCT
a G V D -
2) AGP3-8-2-a
NdeI
TATGTGGGGTGCTTGTTGGCCGTTCCCGTGGGAATGTTTCAAAGAAGGTGGAGGCGGT
1
60
ACACCCCACGAACAACCGGCAAGGGCACCCTTACAAAGTTTCTTCCACCTCCGCCA
a M W G A C W P F P W E C F K E G G G G -
SalI
GGGG
61
69
CCCCAGCT
a G V D -

FIG. 4B

3) AGP3-8-4-a

```
        NdeI
          |
          TATGGTTCCGTTCTGTGACCTGCTGACTAAACACTGTTTCGAAGCTGGTGGAGGCGGT
       1 ---------+---------+---------+---------+---------+---------+ 60
           ACCAAGGCAAGACACTGGACGACTGATTTGTGACAAAGCTTCGACCACCTCCGCCA

a          M  V  P  F  C  D  L  L  T  K  H  C  F  E  A  G  G  G  G  -

         SalI
          |
         GGGG
      61 --------- 69
         CCCCAGCT

a        G  V  D  -
```

4) AGP3-12-4-a

November 6, 2000 12:53 ..

```
        NdeI
          |
          TATGGGTTCTCGTTGTAAATACAAATGGGACGTTCTGACTAAACAGTGTTTCCACCAC
       1 ---------+---------+---------+---------+---------+---------+ 60
           ACCCAAGAGCAACATTTATGTTTACCCTGCAAGACTGATTTGTCACAAAGGTGGTG

a          M  G  S  R  C  K  Y  K  W  D  V  L  T  K  Q  C  F  H  H  -

                   SalI
                    |
         GGTGGAGGCGGTGGGG
      61 ---------+---------+- 81
         CCACCTCCGCCACCCCAGCT

a        G  G  G  G  G  V  D  -
```

FIG. 4C

```
5) AGP3-12-3-a
        NdeI
          |
          TATGCTGCCGGGTTGTAAATGGGACCTGCTGATCAAACAGTGGGTTTGTGACCCGCTG
       1 ---------+---------+---------+---------+---------+---------+ 60
           ACGACGGCCCAACATTTACCCTGGACGACTAGTTTGTCACCCAAACACTGGGCGAC

a          M  L  P  G  C  K  W  D  L  L  I  K  Q  W  V  C  D  P  L  -

                    SalI
                     |
          GGTGGAGGCGGTGGGG
      61 ---------+---------+- 81
          CCACCTCCGCCACCCCAGCT

a         G  G  G  G  G  V  D  -

6) AGP3-12-5-a
          NdeI
          |
          TATGTCTGCTGACTGTTACTTCGACATCCTGACTAAATCTGACGTTTGTACTTCTTCT
       1 ---------+---------+---------+---------+---------+---------+ 60
           ACAGACGACTGACAATGAAGCTGTAGGACTGATTTAGACTGCAAACATGAAGAAGA

a          M  S  A  D  C  Y  F  D  I  L  T  K  S  D  V  C  T  S  S  -

                    SalI
                     |
          GGTGGAGGCGGTGGGG
      61 ---------+---------+- 81
          CCACCTCCGCCACCCCAGCT

a         G  G  G  G  G  V  D  -
```

FIG. 4D

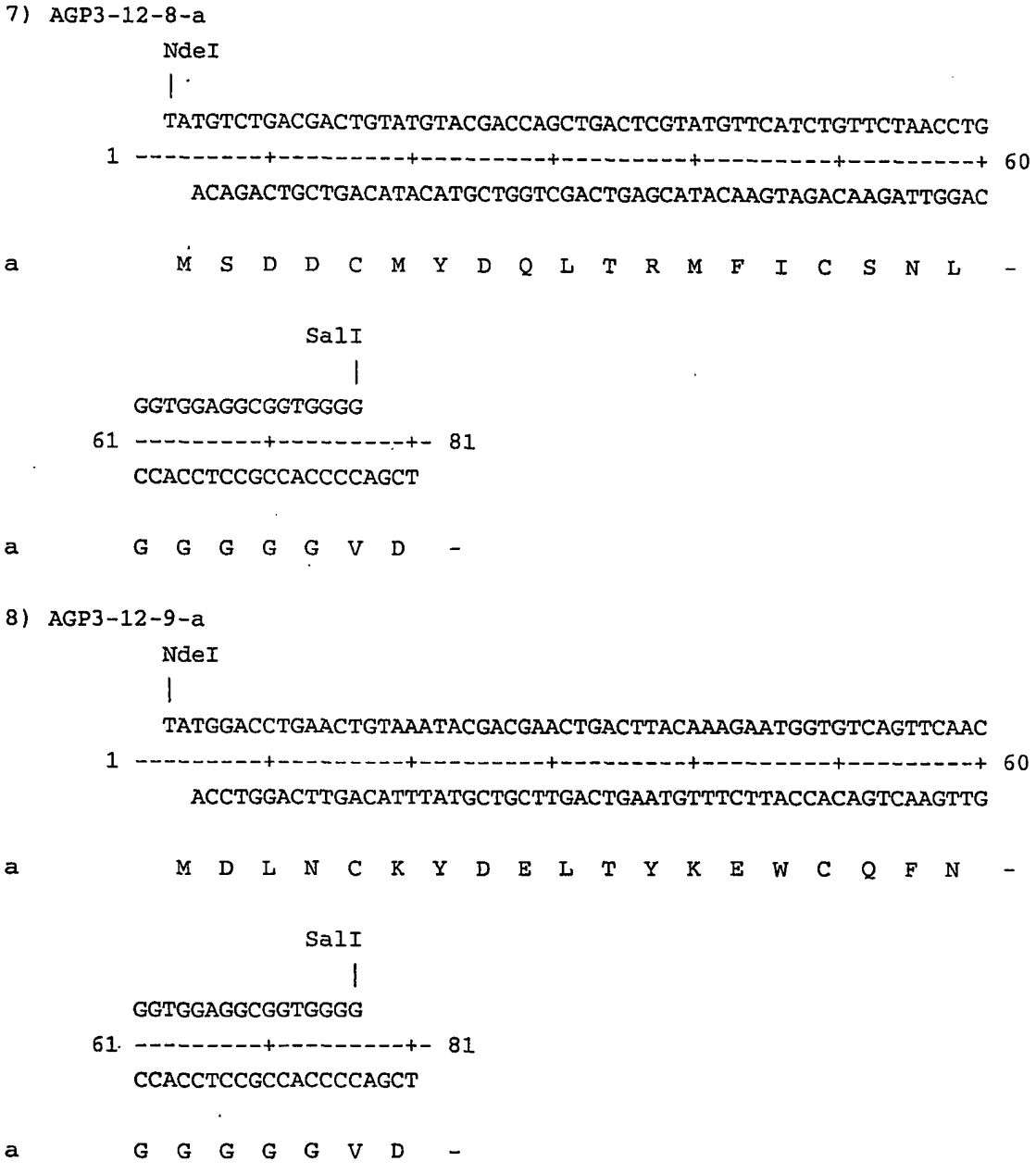

7) AGP3-12-8-a
NdeI
TATGTCTGACGACTGTATGTACGACCAGCTGACTCGTATGTTCATCTGTTCTAACCTG
1
ACAGACTGCTGACATACATGCTGGTCGACTGAGCATACAAGTAGACAAGATTGGAC
60
a M S D D C M Y D Q L T R M F I C S N L -
SalI
GGTGGAGGCGGTGGGG
61
CCACCTCCGCCACCCCAGCT
81
a G G G G G V D -
8) AGP3-12-9-a
NdeI
TATGGACCTGAACTGTAAATACGACGAACTGACTTACAAAGAATGGTGTCAGTTCAAC
1
ACCTGGACTTGACATTTATGCTGCTTGACTGAATGTTTCTTACCACAGTCAAGTTG
60
a M D L N C K Y D E L T Y K E W C Q F N -
SalI
GGTGGAGGCGGTGGGG
61
CCACCTCCGCCACCCCAGCT
81
a G G G G G V D -

FIG. 4E

```
9) AGP3-12-10-a
          NdeI
          |
          TATGTTCCACGACTGTAAATACGACCTGCTGACTCGTCAGATGGTTTGTCACGGTCTG
       1 ---------+---------+---------+---------+---------+---------+ 60
            ACAAGGTGCTGACATTTATGCTGGACGACTGAGCAGTCTACCAAACAGTGCCAGAC

a           M  F  H  D  C  K  Y  D  L  L  T  R  Q  M  V  C  H  G  L  -

                    SalI
                      |
         GGTGGAGGCGGTGGGG
      61 ---------+---------+- 81
         CCACCTCCGCCACCCCAGCT -

a        G  G  G  G  G  V  D  -

10) AGP3-12-11-a
          NdeI
          |
          TATGCGTAACCACTGTTTCTGGGACCACCTGCTGAAACAGGACATCTGTCCGTCTCCG
       1 ---------+---------+---------+---------+---------+---------+ 60
            ACGCATTGGTGACAAAGACCCTGGTGGACGACTTTGTCCTGTAGACAGGCAGAGGC

a           M  R  N  H  C  F  W  D  H  L  L  K  Q  D  I  C  P  S  P  -

                    SalI
                      |
         GGTGGAGGCGGTGGGG
      61 ---------+---------+- 81
         CCACCTCCGCCACCCCAGCT

a        G  G  G  G  G  V  D  -
```

FIG. 4F

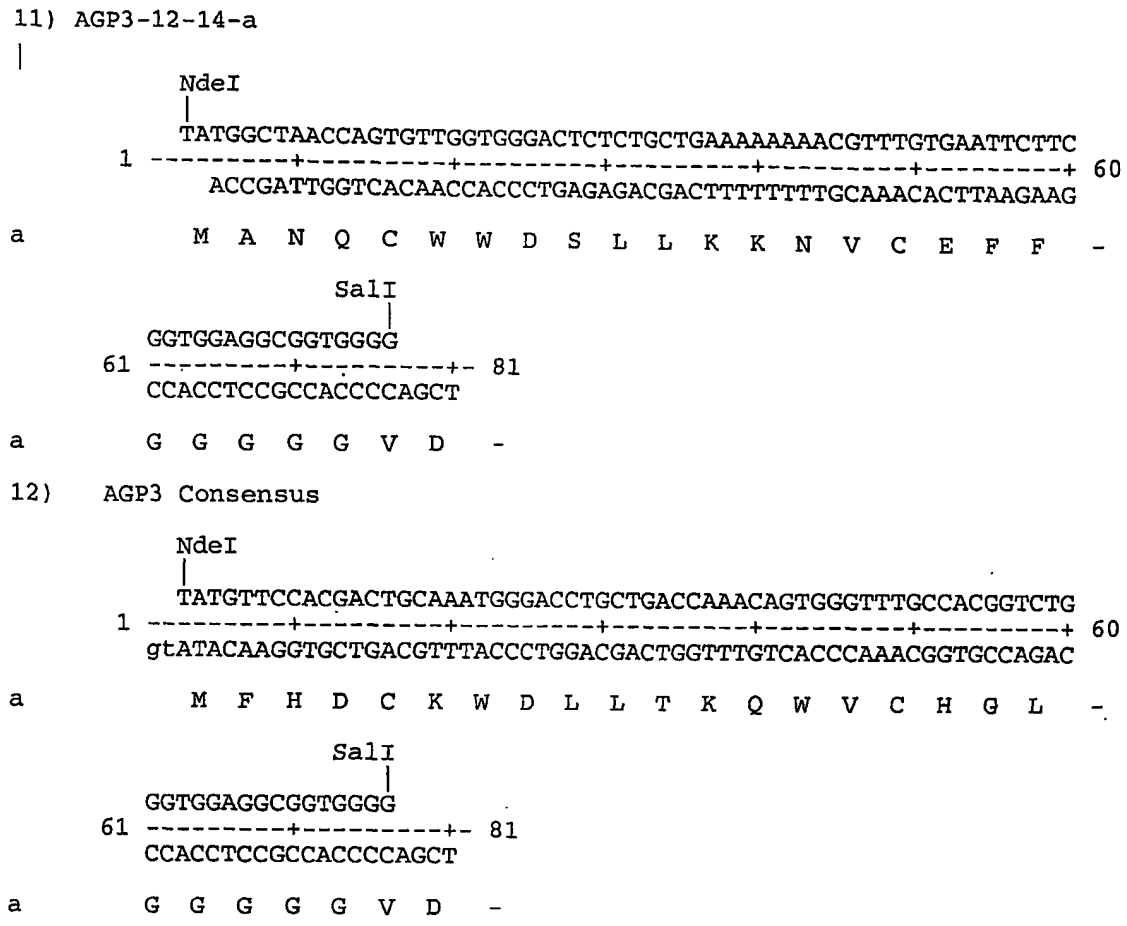

11) AGP3-12-14-a
NdeI
TATGGCTAACCAGTGTTGGTGGGACTCTCTGCTGAAAAAAAACGTTTGTGAATTCTTC
1
ACCGATTGGTCACAACCACCCTGAGAGACGACTTTTTTTTGCAAACACTTAAGAAG
60
a M A N Q C W W D S L L K K N V C E F F -
SalI
GGTGGAGGCGGTGGGG
61
81
CCACCTCCGCCACCCCAGCT
a G G G G G V D -
12) AGP3 Consensus
NdeI
TATGTTCCACGACTGCAAATGGGACCTGCTGACCAAACAGTGGGTTTGCCACGGTCTG
1
60
gtATACAAGGTGCTGACGTTTACCCTGGACGACTGGTTTGTCACCCAAACGGTGCCAGAC
a M F H D C K W D L L T K Q W V C H G L -
SalI
GGTGGAGGCGGTGGGG
61
81
CCACCTCCGCCACCCCAGCT
a G G G G G V D -

FIG. 5A

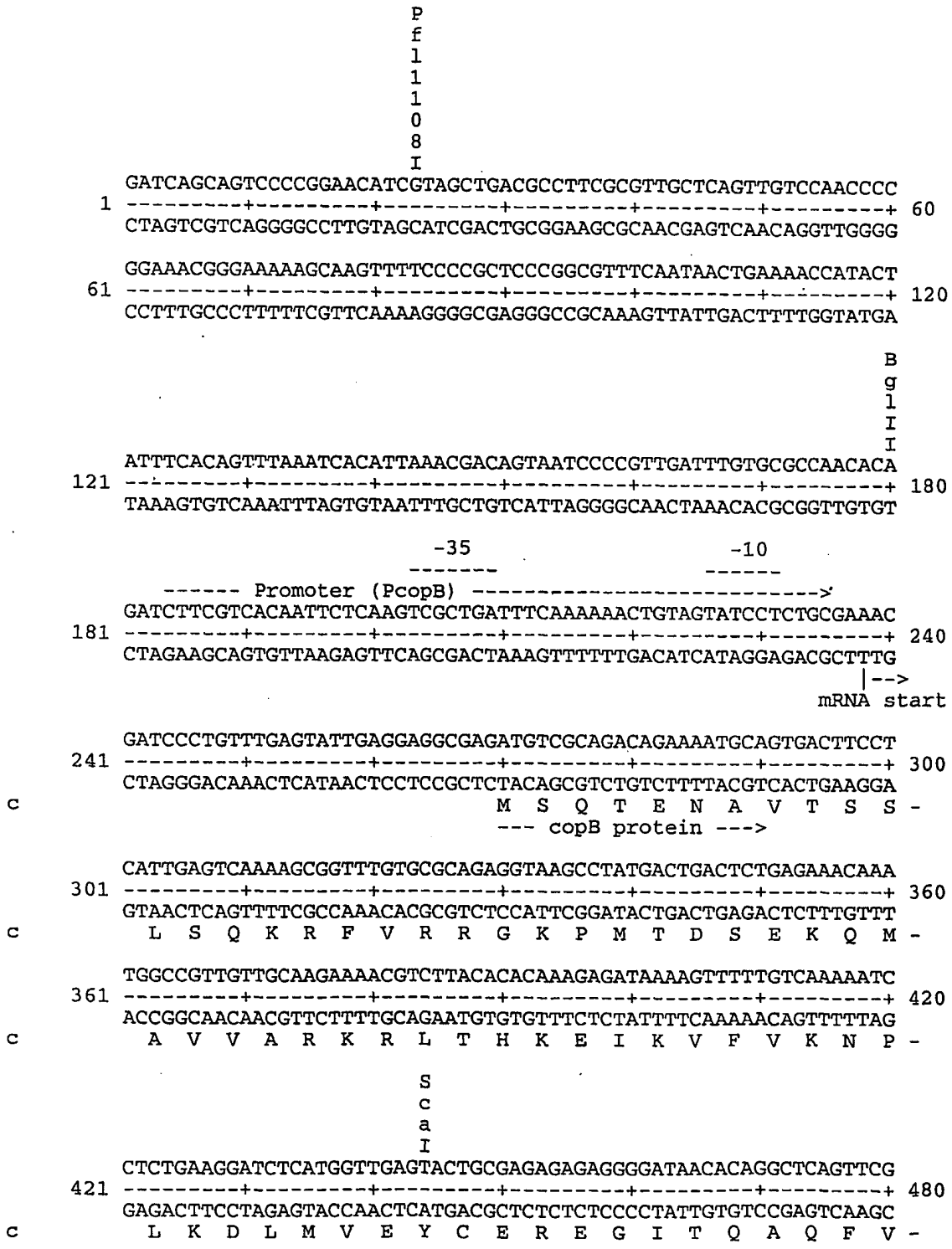

Pfl1108I
BglII
-35
-10
Promoter (PcopB)
mRNA start
M S Q T E N A V T S S -
--- copB protein --->
L S Q K R F V R R G K P M T D S E K Q M -
A V V A R K R L T H K E I K V F V K N P -
ScaI
L K D L M V E Y C E R E G I T Q A Q F V -

FIG. 5B

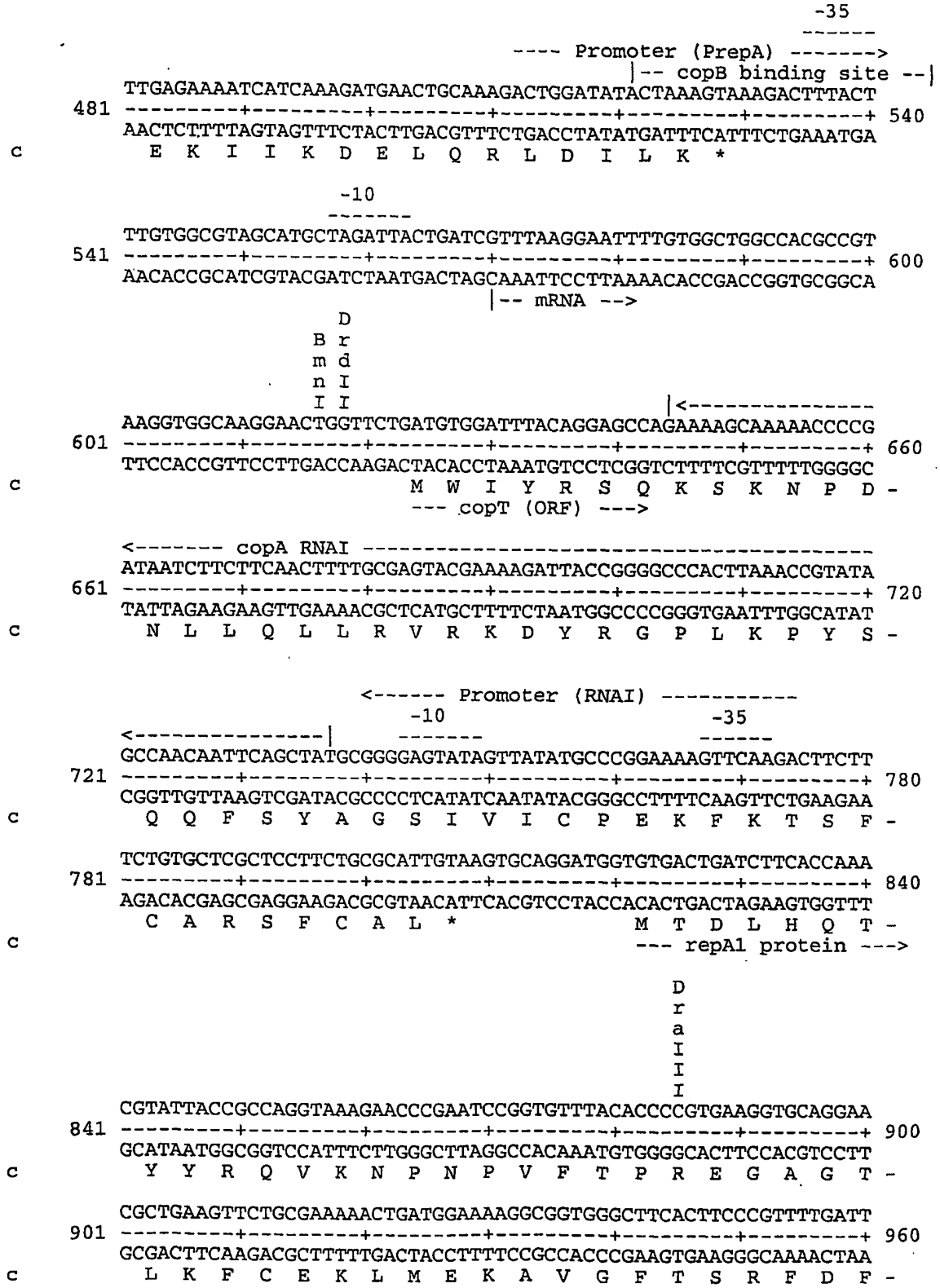
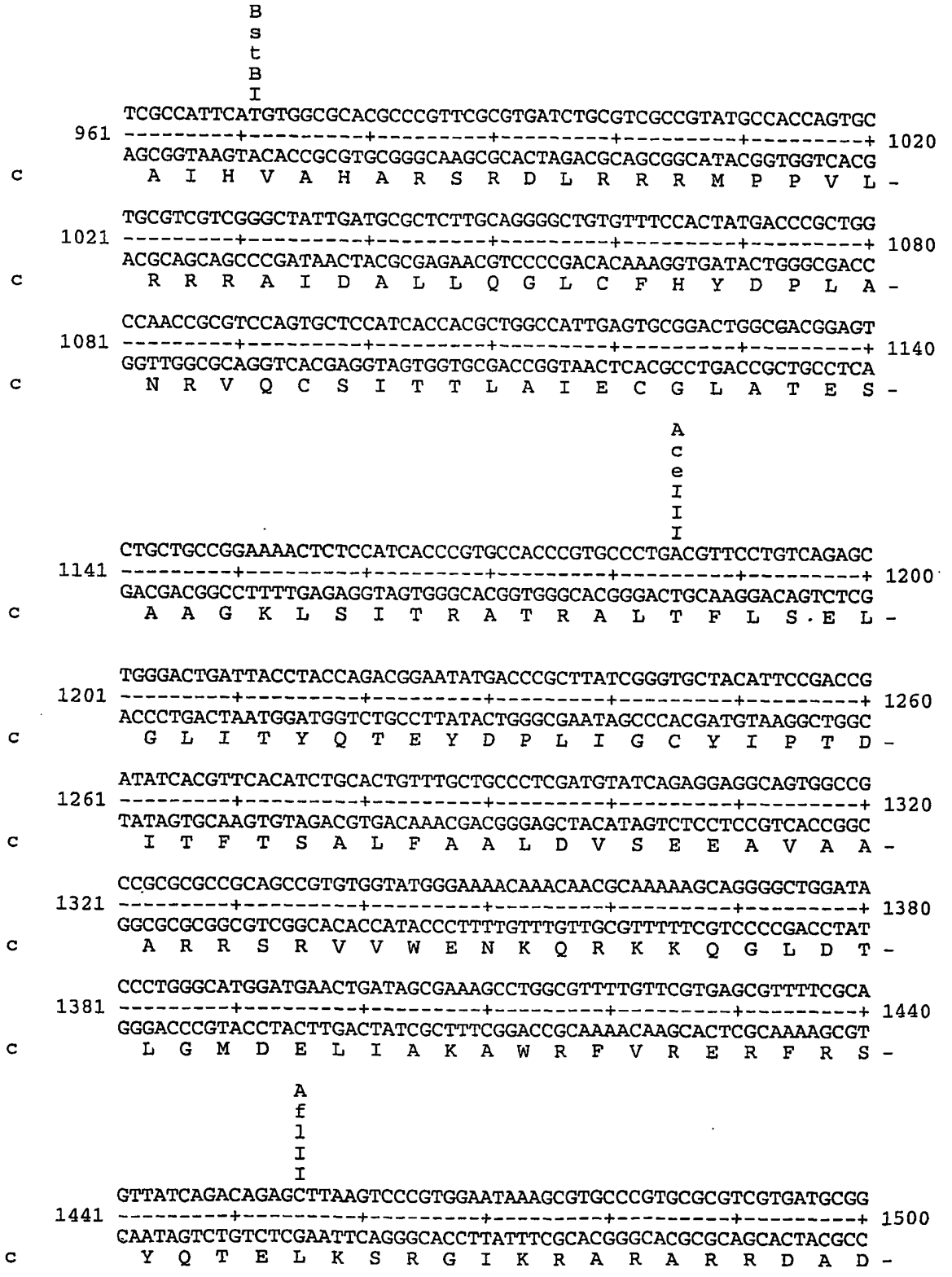

-35
---- Promoter (PrepA) ------->
|-- copB binding site --|
TTGAGAAAATCATCAAAGATGAACTGCAAAGACTGGATATACTAAAGTAAAGACTTTACT
481
AACTCTTTTAGTAGTTTCTACTTGACGTTTCTGACCTATATGATTTCATTTCTGAAATGA 540
c E K I I K D E L Q R L D I L K *
-10
TTGTGGCGTAGCATGCTAGATTACTGATCGTTTAAGGAATTTTGTGGCTGGCCACGCCGT
541
AACACCGCATCGTACGATCTAATGACTAGCAAATTCCTTAAAACACCGACCGGTGCGGCA 600
|-- mRNA -->
D
B r
m d
n I
I I
|<----------
AAGGTGGCAAGGAACTGGTTCTGATGTGGATTTACAGGAGCCAGAAAAGCAAAAACCCCG
601
TTCCACCGTTCCTTGACCAAGACTACACCTAAATGTCCTCGGTCTTTTCGTTTTTGGGGC 660
c M W I Y R S Q K S K N P D -
--- copT (ORF) --->
<------- copA RNAI ----------
ATAATCTTCTTCAACTTTTGCGAGTACGAAAAGATTACCGGGGCCCACTTAAACCGTATA
661
TATTAGAAGAAGTTGAAAACGCTCATGCTTTTCTAATGGCCCCGGGTGAATTTGGCATAT 720
c N L L Q L L R V R K D Y R G P L K P Y S -
<------ Promoter (RNAI) ----------
-10 -35
<---------- ------- ------
GCCAACAATTCAGCTATGCGGGGAGTATAGTTATATGCCCGGAAAAGTTCAAGACTTCTT
721
CGGTTGTTAAGTCGATACGCCCCTCATATCAATATACGGGCCTTTTCAAGTTCTGAAGAA 780
c Q Q F S Y A G S I V I C P E K F K T S F -
TCTGTGCTCGCTCCTTCTGCGCATTGTAAGTGCAGGATGGTGTGACTGATCTTCACCAAA
781
AGACACGAGCGAGGAAGACGCGTAACATTCACGTCCTACCACACTGACTAGAAGTGGTTT 840
C A R S F C A L * M T D L H Q T -
c --- repA1 protein --->
D
r
a
I
I
I
CGTATTACCGCCAGGTAAAGAACCCGAATCCGGTGTTTACACCCCGTGAAGGTGCAGGAA
841
GCATAATGGCGGTCCATTTCTTGGGCTTAGGCCACAAATGTGGGGCACTTCCACGTCCTT 900
c Y Y R Q V K N P N P V F T P R E G A G T -
CGCTGAAGTTCTGCGAAAAACTGATGGAAAAGGCGGTGGGCTTCACTTCCCGTTTTGATT
901
GCGACTTCAAGACGCTTTTTGACTACCTTTTCCGCCACCCGAAGTGAAGGGCAAAACTAA 960
c L K F C E K L M E K A V G F T S R F D F -

FIG. 5C


BstBI
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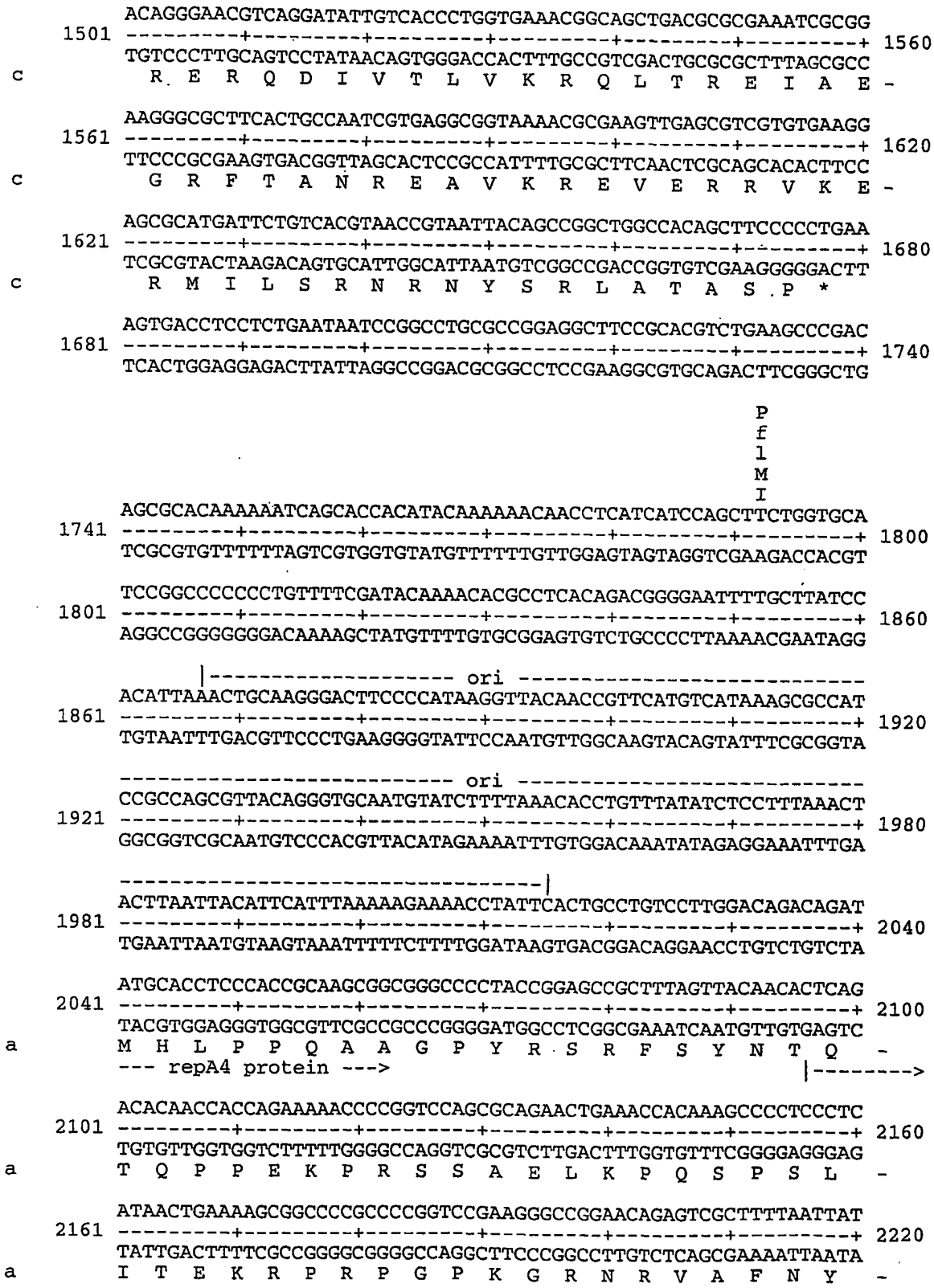
961
AGCGGTAAGTACACCGCGTGCGGGCAAGCGCACTAGACGCAGCGGCATACGGTGGTCACG
1020
c A I H V A H A R S R D L R R R M P P V L -
TGCGTCGTCGGGCTATTGATGCGCTCTTGCAGGGGCTGTGTTTCCACTATGACCCGCTGG
1021
ACGCAGCAGCCCGATAACTACGCGAGAACGTCCCCGACACAAAGGTGATACTGGGCGACC
1080
c R R R A I D A L L Q G L C F H Y D P L A -
CCAACCGCGTCCAGTGCTCCATCACCACGCTGGCCATTGAGTGCGGACTGGCGACGGAGT
1081
GGTTGGCGCAGGTCACGAGGTAGTGGTGCGACCGGTAACTCACGCCTGACCGCTGCCTCA
1140
c N R V Q C S I T T L A I E C G L A T E S -
AceIII
CTGCTGCCGGAAAACTCTCCATCACCCGTGCCACCCGTGCCCTGACGTTCCTGTCAGAGC
1141
GACGACGGCCTTTTGAGAGGTAGTGGGCACGGTGGGCACGGGACTGCAAGGACAGTCTCG
1200
c A A G K L S I T R A T R A L T F L S E L -
TGGGACTGATTACCTACCAGACGGAATATGACCCGCTTATCGGGTGCTACATTCCGACCG
1201
ACCCTGACTAATGGATGGTCTGCCTTATACTGGGCGAATAGCCCACGATGTAAGGCTGGC
1260
c G L I T Y Q T E Y D P L I G C Y I P T D -
ATATCACGTTCACATCTGCACTGTTTGCTGCCCTCGATGTATCAGAGGAGGCAGTGGCCG
1261
TATAGTGCAAGTGTAGACGTGACAAACGACGGGAGCTACATAGTCTCCTCCGTCACCGGC
1320
c I T F T S A L F A A L D V S E E A V A A -
CCGCGCGCCGCAGCCGTGTGGTATGGGAAAACAAACAACGCAAAAAGCAGGGGCTGGATA
1321
GGCGCGCGGCGTCGGCACACCATACCCTTTTGTTTGTTGCGTTTTTCGTCCCCGACCTAT
1380
c A R R S R V V W E N K Q R K K Q G L D T -
CCCTGGGCATGGATGAACTGATAGCGAAAGCCTGGCGTTTTGTTCGTGAGCGTTTTCGCA
1381
GGGACCCGTACCTACTTGACTATCGCTTTCGGACCGCAAAACAAGCACTCGCAAAAGCGT
1440
c L G M D E L I A K A W R F V R E R F R S -
AflIII
GTTATCAGACAGAGCTTAAGTCCCGTGGAATAAAGCGTGCCCGTGCGCGTCGTGATGCGG
1441
CAATAGTCTGTCTCGAATTCAGGGCACCTTATTTCGCACGGGCACGCGCAGCACTACGCC
1500
c Y Q T E L K S R G I K R A R A R R D A D -

FIG. 5D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1501
1560
TGTCCCTTGCAGTCCTATAACAGTGGGACCACTTTGCCGTCGACTGCGCGCTTTAGCGCC
c R E R Q D I V T L V K R Q L T R E I A E -
AAGGGCGCTTCACTGCCAATCGTGAGGCGGTAAAACGCGAAGTTGAGCGTCGTGTGAAGG
1561
1620
TTCCCGCGAAGTGACGGTTAGCACTCCGCCATTTTGCGCTTCAACTCGCAGCACACTTCC
c G R F T A N R E A V K R E V E R R V K E -
AGCGCATGATTCTGTCACGTAACCGTAATTACAGCCGGCTGGCCACAGCTTCCCCCTGAA
1621
1680
TCGCGTACTAAGACAGTGCATTGGCATTAATGTCGGCCGACCGGTGTCGAAGGGGGACTT
c R M I L S R N R N Y S R L A T A S P *
AGTGACCTCCTCTGAATAATCCGGCCTGCGCCGGAGGCTTCCGCACGTCTGAAGCCCGAC
1681
1740
TCACTGGAGGAGACTTATTAGGCCGGACGCGGCCTCCGAAGGCGTGCAGACTTCGGGCTG
P
f
l
M
I
AGCGCACAAAAAATCAGCACCACATACAAAAAACAACCTCATCATCCAGCTTCTGGTGCA
1741
1800
TCGCGTGTTTTTTAGTCGTGGTGTATGTTTTTTGTTGGAGTAGTAGGTCGAAGACCACGT
TCCGGCCCCCCCTGTTTTCGATACAAAACACGCCTCACAGACGGGGAATTTTGCTTATCC
1801
1860
AGGCCGGGGGGGACAAAAGCTATGTTTTGTGCGGAGTGTCTGCCCCTTAAAACGAATAGG
|-------------------- ori ----------
ACATTAAACTGCAAGGGACTTCCCCATAAGGTTACAACCGTTCATGTCATAAAGCGCCAT
1861
1920
TGTAATTTGACGTTCCCTGAAGGGGTATTCCAATGTTGGCAAGTACAGTATTTCGCGGTA
---------- ori ----------
CCGCCAGCGTTACAGGGTGCAATGTATCTTTTAAACACCTGTTTATATCTCCTTTAAACT
1921
1980
GGCGGTCGCAATGTCCCACGTTACATAGAAAATTTGTGGACAAATATAGAGGAAATTTGA
----------|
ACTTAATTACATTCATTTAAAAAGAAAACCTATTCACTGCCTGTCCTTGGACAGACAGAT
1981
2040
TGAATTAATGTAAGTAAATTTTTCTTTTGGATAAGTGACGGACAGGAACCTGTCTGTCTA
ATGCACCTCCCACCGCAAGCGGCGGGCCCCTACCGGAGCCGCTTTAGTTACAACACTCAG
2041
2100
TACGTGGAGGGTGGCGTTCGCCGCCCGGGGATGGCCTCGGCGAAATCAATGTTGTGAGTC
a M H L P P Q A A G P Y R S R F S Y N T Q -
--- repA4 protein --->|-------->
ACACAACCACCAGAAAAACCCCGGTCCAGCGCAGAACTGAAACCACAAAGCCCCTCCCTC
2101
2160
TGTGTTGGTGGTCTTTTTGGGGCCAGGTCGCGTCTTGACTTTGGTGTTTCGGGGAGGGAG
a T Q P P E K P R S S A E L K P Q S P S L -
ATAACTGAAAAGCGGCCCCGCCCCGGTCCGAAGGGCCGGAACAGAGTCGCTTTTAATTAT
2161
2220
TATTGACTTTTCGCCGGGGCGGGGCCAGGCTTCCCGGCCTTGTCTCAGCGAAAATTAATA
a I T E K R P R P G P K G R N R V A F N Y -

FIG. 5E

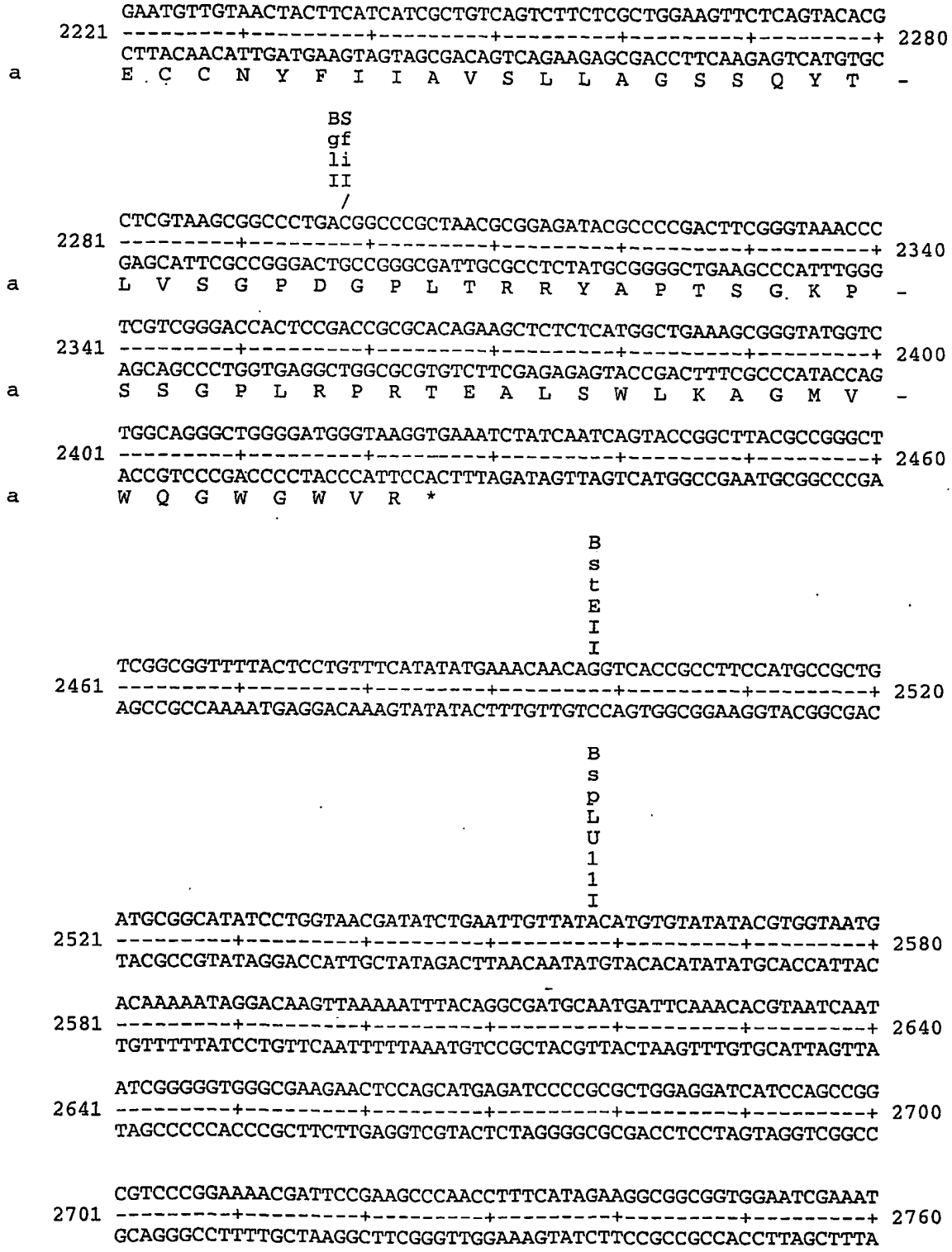
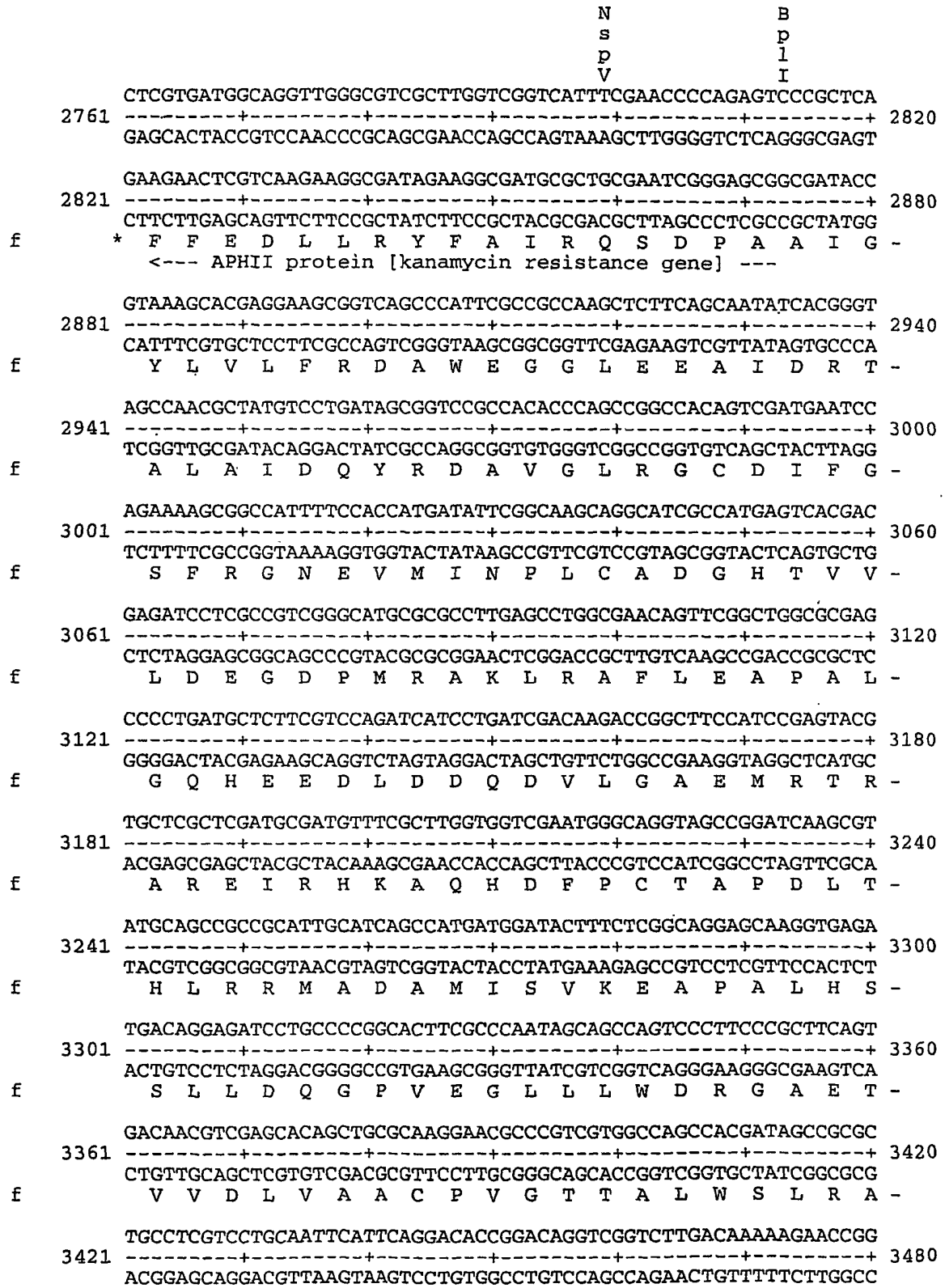

GAATGTTGTAACTACTTCATCATCGCTGTCAGTCTTCTCGCTGGAAGTTCTCAGTACACG
2221
2280
CTTACAACATTGATGAAGTAGTAGCGACAGTCAGAAGAGCGACCTTCAAGAGTCATGTGC
a E C C N Y F I I A V S L L A G S S Q Y T -
BS
gf
li
II
/
CTCGTAAGCGGCCCTGACGGCCCGCTAACGCGGAGATACGCCCCGACTTCGGGTAAACCC
2281
2340
GAGCATTCGCCGGGACTGCCGGGCGATTGCGCCTCTATGCGGGGCTGAAGCCCATTTGGG
a L V S G P D G P L T R R Y A P T S G K P -
TCGTCGGGACCACTCCGACCGCGCACAGAAGCTCTCTCATGGCTGAAAGCGGGTATGGTC
2341
2400
AGCAGCCCTGGTGAGGCTGGCGCGTGTCTTCGAGAGAGTACCGACTTTCGCCCATACCAG
a S S G P L R P R T E A L S W L K A G M V -
TGGCAGGGCTGGGGATGGGTAAGGTGAAATCTATCAATCAGTACCGGCTTACGCCGGGCT
2401
2460
ACCGTCCCGACCCCTACCCATTCCACTTTAGATAGTTAGTCATGGCCGAATGCGGCCCGA
a W Q G W G W V R *
BstEII
TCGGCGGTTTTACTCCTGTTTCATATATGAAACAACAGGTCACCGCCTTCCATGCCGCTG
2461
2520
AGCCGCCAAAATGAGGACAAAGTATATACTTTGTTGTCCAGTGGCGGAAGGTACGGCGAC
BspLU11I
ATGCGGCATATCCTGGTAACGATATCTGAATTGTTATACATGTGTATATACGTGGTAATG
2521
2580
TACGCCGTATAGGACCATTGCTATAGACTTAACAATATGTACACATATATGCACCATTAC
ACAAAAATAGGACAAGTTAAAAATTTACAGGCGATGCAATGATTCAAACACGTAATCAAT
2581
2640
TGTTTTTATCCTGTTCAATTTTTAAATGTCCGCTACGTTACTAAGTTTGTGCATTAGTTA
ATCGGGGGTGGGCGAAGAACTCCAGCATGAGATCCCCGCGCTGGAGGATCATCCAGCCGG
2641
2700
TAGCCCCCACCCGCTTCTTGAGGTCGTACTCTAGGGGCGCGACCTCCTAGTAGGTCGGCC
CGTCCCGGAAAACGATTCCGAAGCCCAACCTTTCATAGAAGGCGGCGGTGGAATCGAAAT
2701
2760
GCAGGGCCTTTTGCTAAGGCTTCGGGTTGGAAAGTATCTTCCGCCGCCACCTTAGCTTTA

FIG. 5F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B p l I
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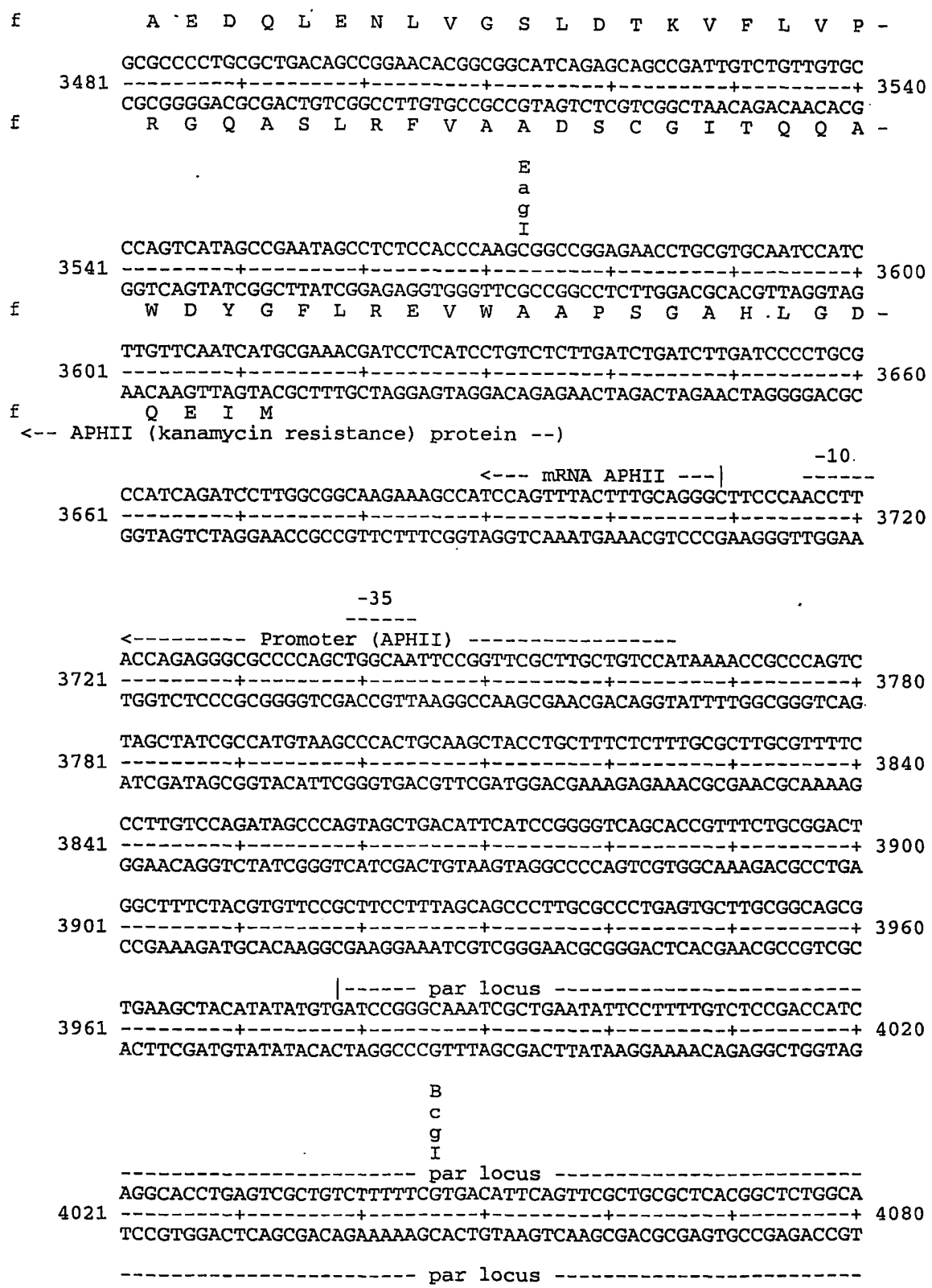
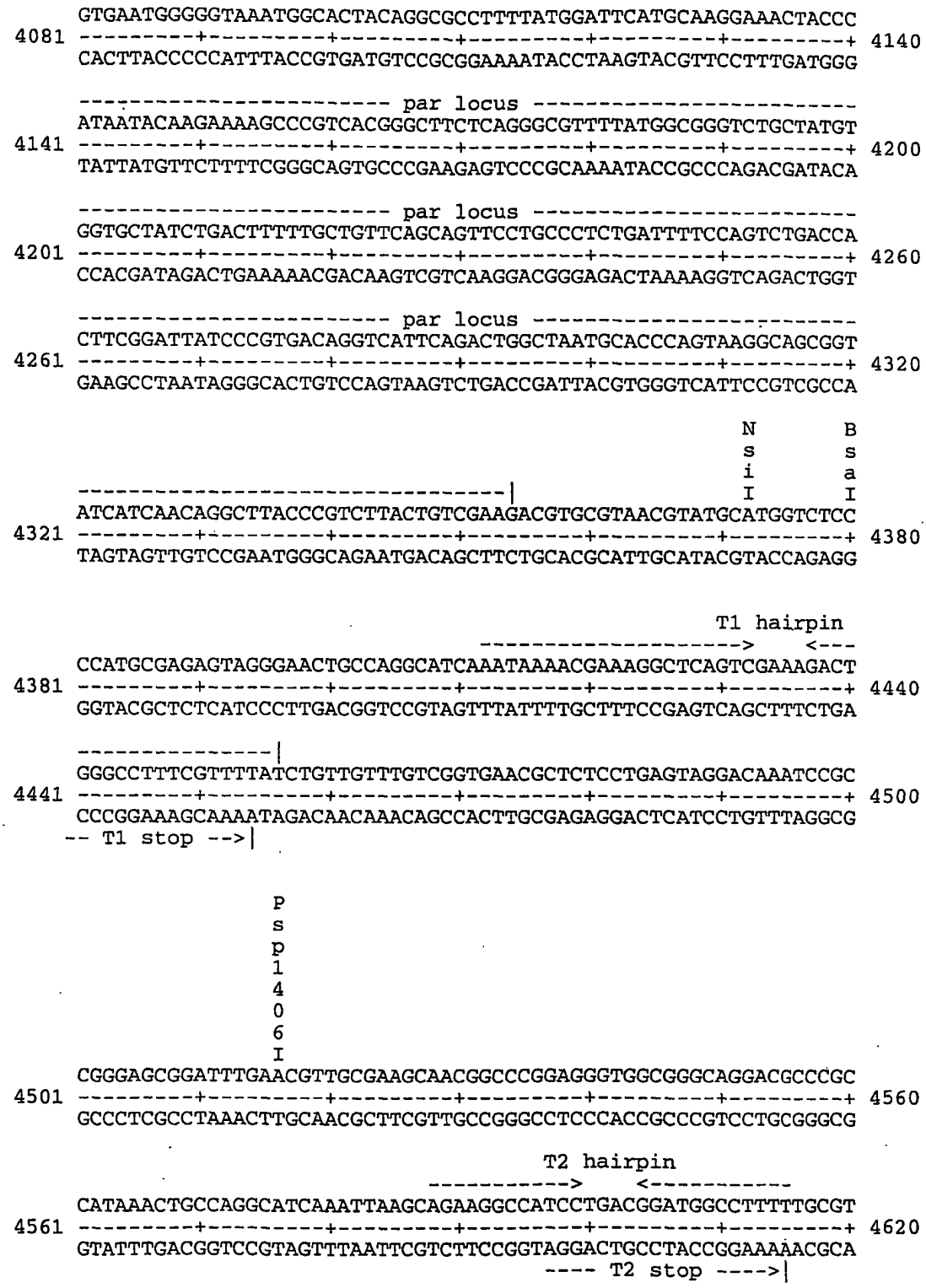
2761
GAGCACTACCGTCCAACCCGCAGCGAACCAGCCAGTAAAGCTTGGGGTCTCAGGGCGAGT
2820
GAAGAACTCGTCAAGAAGGCGATAGAAGGCGATGCGCTGCGAATCGGGAGCGGCGATACC
2821
CTTCTTGAGCAGTTCTTCCGCTATCTTCCGCTACGCGACGCTTAGCCCTCGCCGCTATGG
2880
f * F F E D L L R Y F A I R Q S D P A A I G -
<--- APHII protein [kanamycin resistance gene] ---
GTAAAGCACGAGGAAGCGGTCAGCCCATTCGCCGCCAAGCTCTTCAGCAATATCACGGGT
2881
CATTTCGTGCTCCTTCGCCAGTCGGGTAAGCGGCGGTTCGAGAAGTCGTTATAGTGCCCA
2940
f Y L V L F R D A W E G G L E E A I D R T -
AGCCAACGCTATGTCCTGATAGCGGTCCGCCACACCCAGCCGGCCACAGTCGATGAATCC
2941
TCGGTTGCGATACAGGACTATCGCCAGGCGGTGTGGGTCGGCCGGTGTCAGCTACTTAGG
3000
f A L A I D Q Y R D A V G L R G C D I F G -
AGAAAAGCGGCCATTTTCCACCATGATATTCGGCAAGCAGGCATCGCCATGAGTCACGAC
3001
TCTTTTCGCCGGTAAAAGGTGGTACTATAAGCCGTTCGTCCGTAGCGGTACTCAGTGCTG
3060
f S F R G N E V M I N P L C A D G H T V V -
GAGATCCTCGCCGTCGGGCATGCGCGCCTTGAGCCTGGCGAACAGTTCGGCTGGCGCGAG
3061
CTCTAGGAGCGGCAGCCCGTACGCGCGGAACTCGGACCGCTTGTCAAGCCGACCGCGCTC
3120
f L D E G D P M R A K L R A F L E A P A L -
CCCCTGATGCTCTTCGTCCAGATCATCCTGATCGACAAGACCGGCTTCCATCCGAGTACG
3121
GGGGACTACGAGAAGCAGGTCTAGTAGGACTAGCTGTTCTGGCCGAAGGTAGGCTCATGC
3180
f G Q H E E D L D D Q D V L G A E M R T R -
TGCTCGCTCGATGCGATGTTTCGCTTGGTGGTCGAATGGGCAGGTAGCCGGATCAAGCGT
3181
ACGAGCGAGCTACGCTACAAAGCGAACCACCAGCTTACCCGTCCATCGGCCTAGTTCGCA
3240
f A R E I R H K A Q H D F P C T A P D L T -
ATGCAGCCGCCGCATTGCATCAGCCATGATGGATACTTTCTCGGCAGGAGCAAGGTGAGA
3241
TACGTCGGCGGCGTAACGTAGTCGGTACTACCTATGAAAGAGCCGTCCTCGTTCCACTCT
3300
f H L R R M A D A M I S V K E A P A L H S -
TGACAGGAGATCCTGCCCCGGCACTTCGCCCAATAGCAGCCAGTCCCTTCCCGCTTCAGT
3301
ACTGTCCTCTAGGACGGGGCCGTGAAGCGGGTTATCGTCGGTCAGGGAAGGGCGAAGTCA
3360
f S L L D Q G P V E G L L L W D R G A E T -
GACAACGTCGAGCACAGCTGCGCAAGGAACGCCCGTCGTGGCCAGCCACGATAGCCGCGC
3361
CTGTTGCAGCTCGTGTCGACGCGTTCCTTGCGGGCAGCACCGGTCGGTGCTATCGGCGCG
3420
f V V D L V A A C P V G T T A L W S L R A -
TGCCTCGTCCTGCAATTCATTCAGGACACCGGACAGGTCGGTCTTGACAAAAAGAACCGG
3421
ACGGAGCAGGACGTTAAGTAAGTCCTGTGGCCTGTCCAGCCAGAACTGTTTTTCTTGGCC
3480

FIG. 5G


f A E D Q L E N L V G S L D T K V F L V P -
GCGCCCCTGCGCTGACAGCCGGAACACGGCGGCATCAGAGCAGCCGATTGTCTGTTGTGC
3481 ---------+---------+---------+---------+---------+---------+ 3540
CGCGGGGACGCGACTGTCGGCCTTGTGCCGCCGTAGTCTCGTCGGCTAACAGACAACACG
f R G Q A S L R F V A A D S C G I T Q Q A -
E
a
g
I
CCAGTCATAGCCGAATAGCCTCTCCACCCAAGCGGCCGGAGAACCTGCGTGCAATCCATC
3541 ---------+---------+---------+---------+---------+---------+ 3600
GGTCAGTATCGGCTTATCGGAGAGGTGGGTTCGCCGGCCTCTTGGACGCACGTTAGGTAG
f W D Y G F L R E V W A A P S G A H L G D -
TTGTTCAATCATGCGAAACGATCCTCATCCTGTCTCTTGATCTGATCTTGATCCCCTGCG
3601 ---------+---------+---------+---------+---------+---------+ 3660
AACAAGTTAGTACGCTTTGCTAGGAGTAGGACAGAGAACTAGACTAGAACTAGGGGACGC
f Q E I M
<-- APHII (kanamycin resistance) protein --)
-10
<--- mRNA APHII ---| ------
CCATCAGATCCTTGGCGGCAAGAAAGCCATCCAGTTTACTTTGCAGGGCTTCCCAACCTT
3661 ---------+---------+---------+---------+---------+---------+ 3720
GGTAGTCTAGGAACCGCCGTTCTTTCGGTAGGTCAAATGAAACGTCCCGAAGGGTTGGAA
-35

<---------- Promoter (APHII) ----------
ACCAGAGGGCGCCCCAGCTGGCAATTCCGGTTCGCTTGCTGTCCATAAAACCGCCCAGTC
3721 ---------+---------+---------+---------+---------+---------+ 3780
TGGTCTCCCGCGGGGTCGACCGTTAAGGCCAAGCGAACGACAGGTATTTTGGCGGGTCAG
TAGCTATCGCCATGTAAGCCCACTGCAAGCTACCTGCTTTCTCTTTGCGCTTGCGTTTTC
3781 ---------+---------+---------+---------+---------+---------+ 3840
ATCGATAGCGGTACATTCGGGTGACGTTCGATGGACGAAAGAGAAACGCGAACGCAAAAG
CCTTGTCCAGATAGCCCAGTAGCTGACATTCATCCGGGGTCAGCACCGTTTCTGCGGACT
3841 ---------+---------+---------+---------+---------+---------+ 3900
GGAACAGGTCTATCGGGTCATCGACTGTAAGTAGGCCCCAGTCGTGGCAAAGACGCCTGA
GGCTTTCTACGTGTTCCGCTTCCTTTAGCAGCCCTTGCGCCCTGAGTGCTTGCGGCAGCG
3901 ---------+---------+---------+---------+---------+---------+ 3960
CCGAAAGATGCACAAGGCGAAGGAAATCGTCGGGAACGCGGGACTCACGAACGCCGTCGC
|------ par locus ------------------------
TGAAGCTACATATATGTGATCCGGGCAAATCGCTGAATATTCCTTTTGTCTCCGACCATC
3961 ---------+---------+---------+---------+---------+---------+ 4020
ACTTCGATGTATATACACTAGGCCCGTTTAGCGACTTATAAGGAAAACAGAGGCTGGTAG
B
c
g
I
------------------------ par locus ------------------------
AGGCACCTGAGTCGCTGTCTTTTTCGTGACATTCAGTTCGCTGCGCTCACGGCTCTGGCA
4021 ---------+---------+---------+---------+---------+---------+ 4080
TCCGTGGACTCAGCGACAGAAAAAGCACTGTAAGTCAAGCGACGCGAGTGCCGAGACCGT
------------------------ par locus ------------------------

FIG. 5H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4081
4140
CACTTACCCCCATTTACCGTGATGTCCGCGGAAAATACCTAAGTACGTTCCTTTGATGGG
par locus
ATAATACAAGAAAAGCCCGTCACGGGCTTCTCAGGGCGTTTTATGGCGGGTCTGCTATGT
4141
4200
TATTATGTTCTTTTCGGGCAGTGCCCGAAGAGTCCCGCAAAATACCGCCCAGACGATACA
par locus
GGTGCTATCTGACTTTTTGCTGTTCAGCAGTTCCTGCCCTCTGATTTTCCAGTCTGACCA
4201
4260
CCACGATAGACTGAAAAACGACAAGTCGTCAAGGACGGGAGACTAAAAGGTCAGACTGGT
par locus
CTTCGGATTATCCCGTGACAGGTCATTCAGACTGGCTAATGCACCCAGTAAGGCAGCGGT
4261
4320
GAAGCCTAATAGGGCACTGTCCAGTAAGTCTGACCGATTACGTGGGTCATTCCGTCGCCA
N
s
i
I
B
s
a
I
ATCATCAACAGGCTTACCCGTCTTACTGTCGAAGACGTGCGTAACGTATGCATGGTCTCC
4321
4380
TAGTAGTTGTCCGAATGGGCAGAATGACAGCTTCTGCACGCATTGCATACGTACCAGAGG
T1 hairpin
CCATGCGAGAGTAGGGAACTGCCAGGCATCAAATAAAACGAAAGGCTCAGTCGAAAGACT
4381
4440
GGTACGCTCTCATCCCTTGACGGTCCGTAGTTTATTTTGCTTTCCGAGTCAGCTTTCTGA
GGGCCTTTCGTTTTATCTGTTGTTTGTCGGTGAACGCTCTCCTGAGTAGGACAAATCCGC
4441
4500
CCCGGAAAGCAAAATAGACAACAAACAGCCACTTGCGAGAGGACTCATCCTGTTTAGGCG
-- T1 stop -->|
P
s
p
1
4
0
6
I
CGGGAGCGGATTTGAACGTTGCGAAGCAACGGCCCGGAGGGTGGCGGGCAGGACGCCCGC
4501
4560
GCCCTCGCCTAAACTTGCAACGCTTCGTTGCCGGGCCTCCCACCGCCCGTCCTGCGGGCG
T2 hairpin
CATAAACTGCCAGGCATCAAATTAAGCAGAAGGCCATCCTGACGGATGGCCTTTTTGCGT
4561
4620
GTATTTGACGGTCCGTAGTTTAATTCGTCTTCCGGTAGGACTGCCTACCGGAAAAACGCA
---- T2 stop ---->|

FIG. 5I

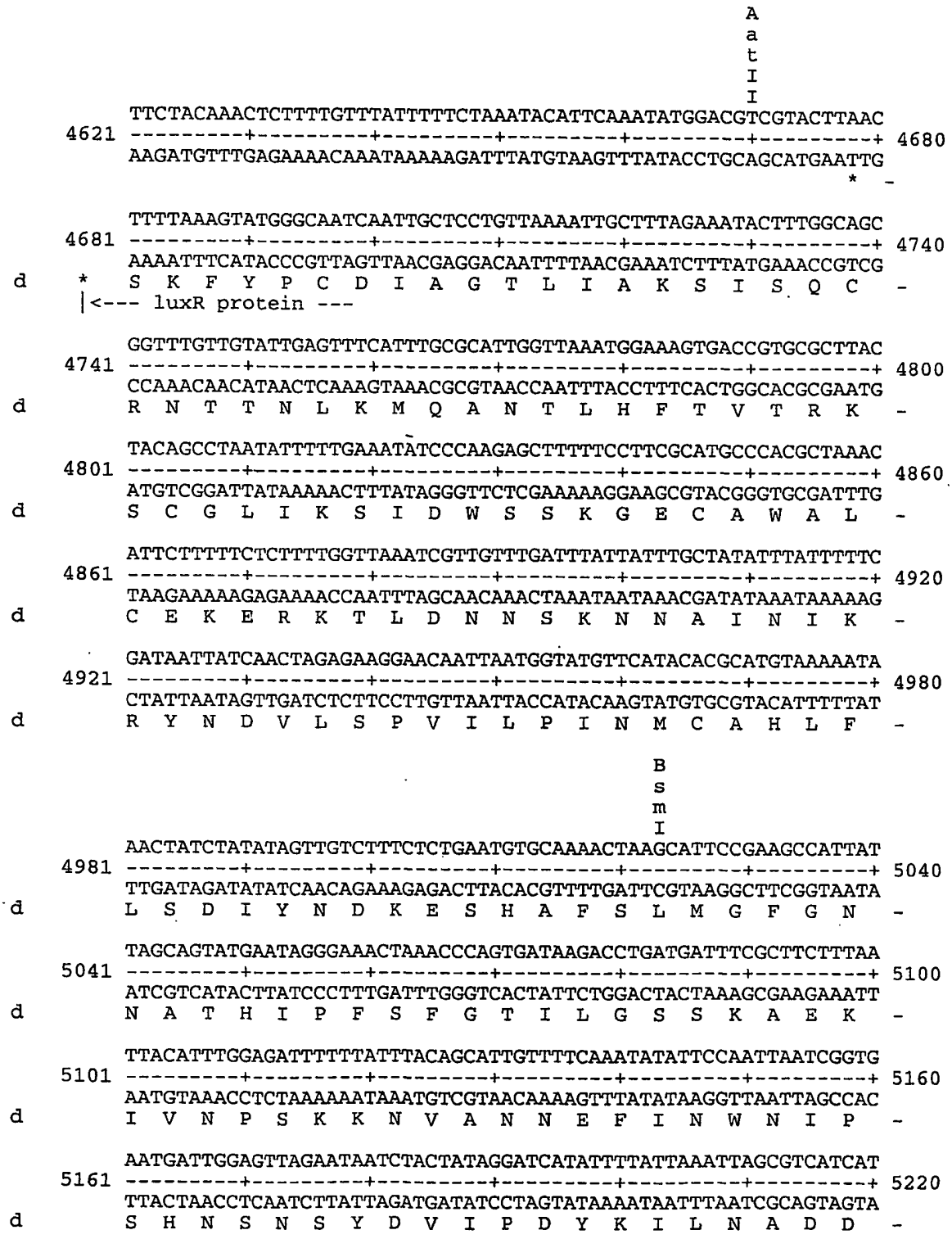
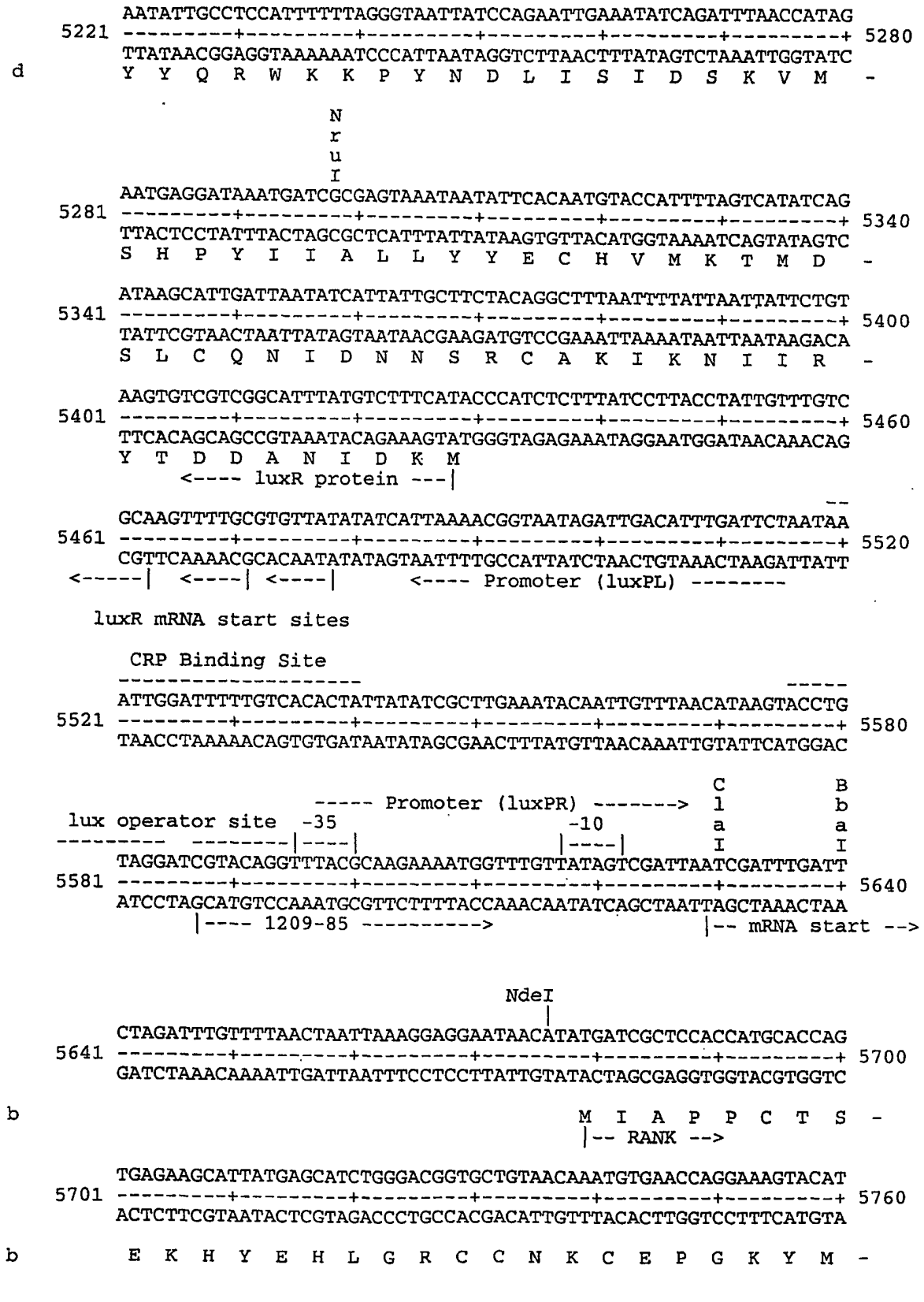

AatII
TTCTACAAACTCTTTTGTTTATTTTTCTAAATACATTCAAATATGGACGTCGTACTTAAC
4621
AAGATGTTTGAGAAAACAAATAAAAAGATTTATGTAAGTTTATACCTGCAGCATGAATTG
4680
TTTTAAAGTATGGGCAATCAATTGCTCCTGTTAAAATTGCTTTAGAAATACTTTGGCAGC
4681
AAAATTTCATACCCGTTAGTTAACGAGGACAATTTTAACGAAATCTTTATGAAACCGTCG
4740
d * S K F Y P C D I A G T L I A K S I S Q C -
|<--- luxR protein ---
GGTTTGTTGTATTGAGTTTCATTTGCGCATTGGTTAAATGGAAAGTGACCGTGCGCTTAC
4741
CCAAACAACATAACTCAAAGTAAACGCGTAACCAATTTACCTTTCACTGGCACGCGAATG
4800
d R N T T N L K M Q A N T L H F T V T R K -
TACAGCCTAATATTTTTGAAATATCCCAAGAGCTTTTTCCTTCGCATGCCCACGCTAAAC
4801
ATGTCGGATTATAAAAACTTTATAGGGTTCTCGAAAAAGGAAGCGTACGGGTGCGATTTG
4860
d S C G L I K S I D W S S K G E C A W A L -
ATTCTTTTTCTCTTTTGGTTAAATCGTTGTTTGATTTATTATTTGCTATATTTATTTTTC
4861
TAAGAAAAAGAGAAAACCAATTTAGCAACAAACTAAATAATAAACGATATAAATAAAAAG
4920
d C E K E R K T L D N N S K N N A I N I K -
GATAATTATCAACTAGAGAAGGAACAATTAATGGTATGTTCATACACGCATGTAAAAATA
4921
CTATTAATAGTTGATCTCTTCCTTGTTAATTACCATACAAGTATGTGCGTACATTTTTAT
4980
d R Y N D V L S P V I L P I N M C A H L F -
BsmI
AACTATCTATATAGTTGTCTTTCTCTGAATGTGCAAAACTAAGCATTCCGAAGCCATTAT
4981
TTGATAGATATATCAACAGAAAGAGACTTACACGTTTTGATTCGTAAGGCTTCGGTAATA
5040
d L S D I Y N D K E S H A F S L M G F G N -
TAGCAGTATGAATAGGGAAACTAAACCCAGTGATAAGACCTGATGATTTCGCTTCTTTAA
5041
ATCGTCATACTTATCCCTTTGATTTGGGTCACTATTCTGGACTACTAAAGCGAAGAAATT
5100
d N A T H I P F S F G T I L G S S K A E K -
TTACATTTGGAGATTTTTTATTTACAGCATTGTTTTCAAATATATTCCAATTAATCGGTG
5101
AATGTAAACCTCTAAAAAATAAATGTCGTAACAAAAGTTTATATAAGGTTAATTAGCCAC
5160
d I V N P S K K N V A N N E F I N W N I P -
AATGATTGGAGTTAGAATAATCTACTATAGGATCATATTTTATTAAATTAGCGTCATCAT
5161
TTACTAACCTCAATCTTATTAGATGATATCCTAGTATAAAATAATTTAATCGCAGTAGTA
5220
d S H N S N S Y D V I P D Y K I L N A D D -

FIG. 5J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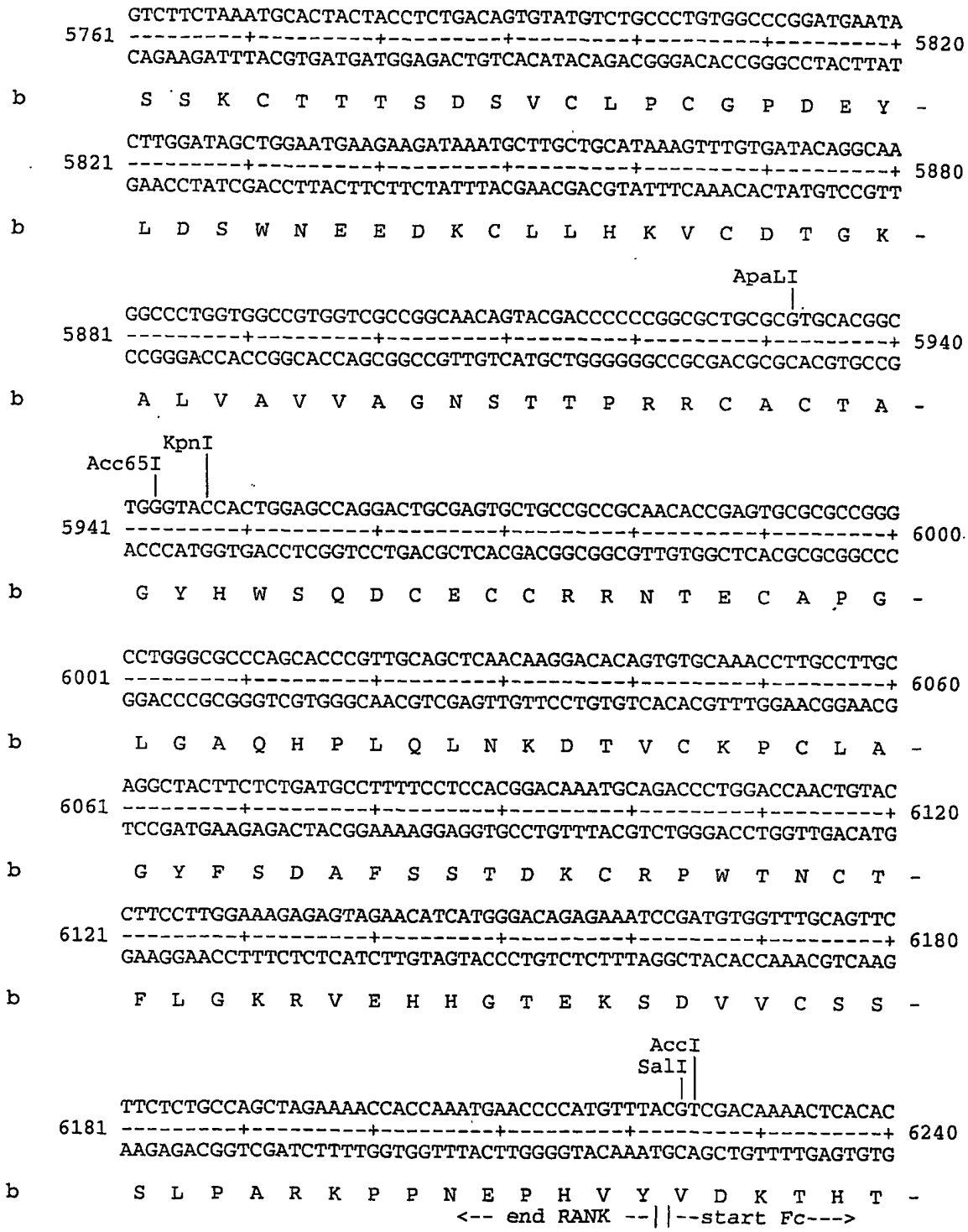
5221
5280
TTATAACGGAGGTAAAAAATCCCATTAATAGGTCTTAACTTTATAGTCTAAATTGGTATC
d
Y Y Q R W K K P Y N D L I S I D S K V M -
N
r
u
I
AATGAGGATAAATGATCGCGAGTAAATAATATTCACAATGTACCATTTTAGTCATATCAG
5281
5340
TTACTCCTATTTACTAGCGCTCATTTATTATAAGTGTTACATGGTAAAATCAGTATAGTC
S H P Y I I A L L Y Y E C H V M K T M D -
ATAAGCATTGATTAATATCATTATTGCTTCTACAGGCTTTAATTTTATTAATTATTCTGT
5341
5400
TATTCGTAACTAATTATAGTAATAACGAAGATGTCCGAAATTAAAATAATTAATAAGACA
S L C Q N I D N N S R C A K I K N I I R -
AAGTGTCGTCGGCATTTATGTCTTTCATACCCATCTCTTTATCCTTACCTATTGTTTGTC
5401
5460
TTCACAGCAGCCGTAAATACAGAAAGTATGGGTAGAGAAATAGGAATGGATAACAAACAG
Y T D D A N I D K M
<---- luxR protein ---|
GCAAGTTTTGCGTGTTATATATCATTAAAACGGTAATAGATTGACATTTGATTCTAATAA
5461
5520
CGTTCAAAACGCACAATATATAGTAATTTTGCCATTATCTAACTGTAAACTAAGATTATT
<-----| <----| <----| <---- Promoter (luxPL) --------
luxR mRNA start sites
CRP Binding Site
ATTGGATTTTTGTCACACTATTATATCGCTTGAAATACAATTGTTTAACATAAGTACCTG
5521
5580
TAACCTAAAAACAGTGTGATAATATAGCGAACTTTATGTTAACAAATTGTATTCATGGAC
C B
----- Promoter (luxPR) -------> l b
lux operator site -35 -10 a a
I I
TAGGATCGTACAGGTTTACGCAAGAAAATGGTTTGTTATAGTCGATTAATCGATTTGATT
5581
5640
ATCCTAGCATGTCCAAATGCGTTCTTTTACCAAACAATATCAGCTAATTAGCTAAACTAA
|---- 1209-85 ----------> |-- mRNA start -->
NdeI
CTAGATTTGTTTTAACTAATTAAAGGAGGAATAACATATGATCGCTCCACCATGCACCAG
5641
5700
GATCTAAACAAAATTGATTAATTTCCTCCTTATTGTATACTAGCGAGGTGGTACGTGGTC
b
M I A P P C T S -
|-- RANK -->
TGAGAAGCATTATGAGCATCTGGGACGGTGCTGTAACAAATGTGAACCAGGAAAGTACAT
5701
5760
ACTCTTCGTAATACTCGTAGACCCTGCCACGACATTGTTTACACTTGGTCCTTTCATGTA
b
E K H Y E H L G R C C N K C E P G K Y M -

FIG. 5K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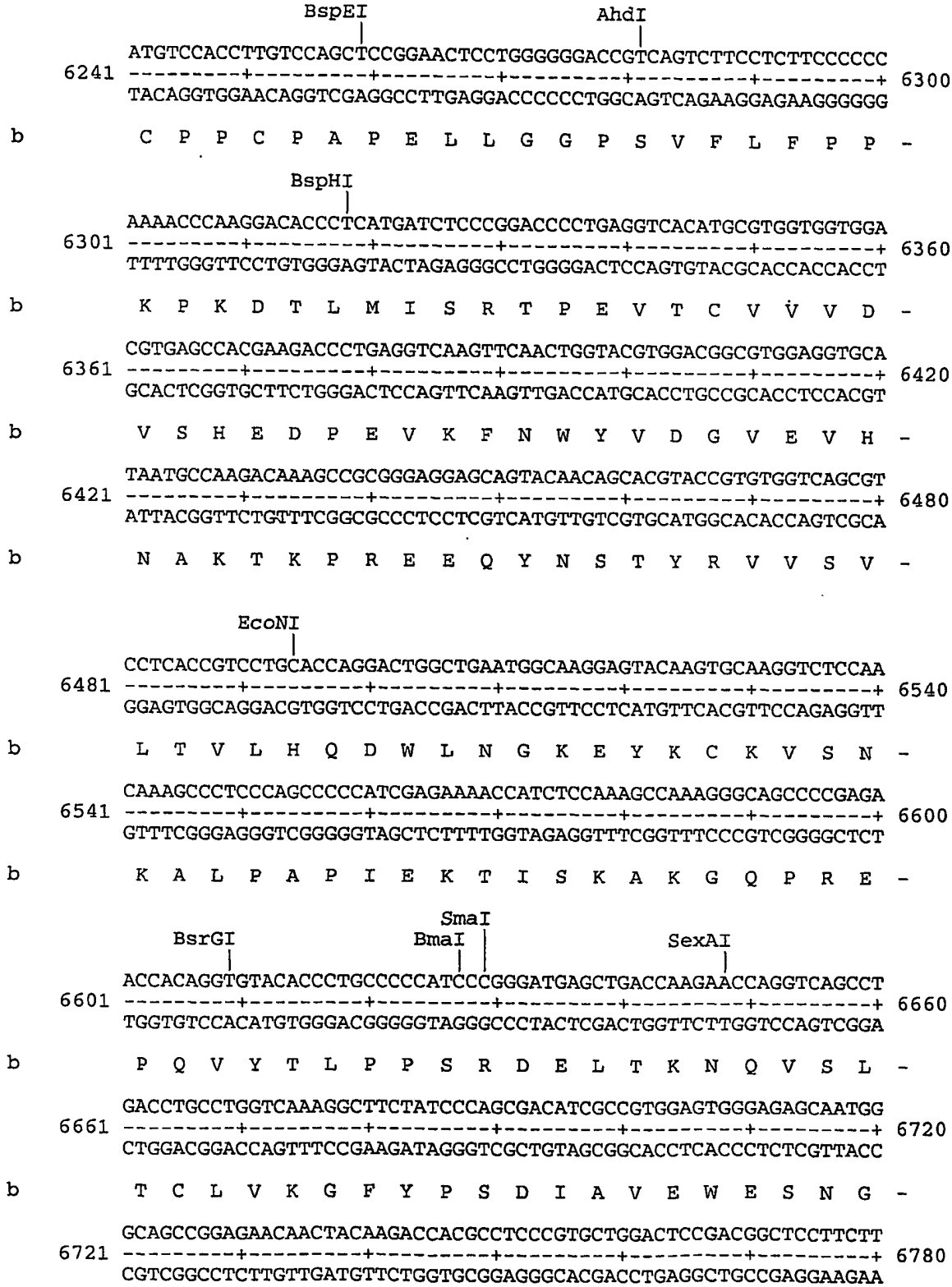
5761
CAGAAGATTTACGTGATGATGGAGACTGTCACATACAGACGGGACACCGGGCCTACTTAT
5820
b S S K C T T T S D S V C L P C G P D E Y -
CTTGGATAGCTGGAATGAAGAAGATAAATGCTTGCTGCATAAAGTTTGTGATACAGGCAA
5821
GAACCTATCGACCTTACTTCTTCTATTTACGAACGACGTATTTCAAACACTATGTCCGTT
5880
b L D S W N E E D K C L L H K V C D T G K -
ApaLI
GGCCCTGGTGGCCGTGGTCGCCGGCAACAGTACGACCCCCCGGCGCTGCGCGTGCACGGC
5881
CCGGGACCACCGGCACCAGCGGCCGTTGTCATGCTGGGGGGCCGCGACGCGCACGTGCCG
5940
b A L V A V V A G N S T T P R R C A C T A -
KpnI
Acc65I
TGGGTACCACTGGAGCCAGGACTGCGAGTGCTGCCGCCGCAACACCGAGTGCGCGCCGGG
5941
ACCCATGGTGACCTCGGTCCTGACGCTCACGACGGCGGCGTTGTGGCTCACGCGCGGCCC
6000
b G Y H W S Q D C E C C R R N T E C A P G -
CCTGGGCGCCCAGCACCCGTTGCAGCTCAACAAGGACACAGTGTGCAAACCTTGCCTTGC
6001
GGACCCGCGGGTCGTGGGCAACGTCGAGTTGTTCCTGTGTCACACGTTTGGAACGGAACG
6060
b L G A Q H P L Q L N K D T V C K P C L A -
AGGCTACTTCTCTGATGCCTTTTCCTCCACGGACAAATGCAGACCCTGGACCAACTGTAC
6061
TCCGATGAAGAGACTACGGAAAAGGAGGTGCCTGTTTACGTCTGGGACCTGGTTGACATG
6120
b G Y F S D A F S S T D K C R P W T N C T -
CTTCCTTGGAAAGAGAGTAGAACATCATGGGACAGAGAAATCCGATGTGGTTTGCAGTTC
6121
GAAGGAACCTTTCTCTCATCTTGTAGTACCCTGTCTCTTTAGGCTACACCAAACGTCAAG
6180
b F L G K R V E H H G T E K S D V V C S S -
AccI
SalI
TTCTCTGCCAGCTAGAAAACCACCAAATGAACCCCATGTTTACGTCGACAAAACTCACAC
6181
AAGAGACGGTCGATCTTTTGGTGGTTTACTTGGGGTACAAATGCAGCTGTTTTGAGTGTG
6240
b S L P A R K P P N E P H V Y V D K T H T -
<-- end RANK --||--start Fc-->

FIG. 5L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6241
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6300
b C P P C P A P E L L G G P S V F L F P P -
BspHI
AAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGA
6301
TTTTGGGTTCCTGTGGGAGTACTAGAGGGCCTGGGGACTCCAGTGTACGCACCACCACCT
6360
b K P K D T L M I S R T P E V T C V V V D -
CGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCA
6361
GCACTCGGTGCTTCTGGGACTCCAGTTCAAGTTGACCATGCACCTGCCGCACCTCCACGT
6420
b V S H E D P E V K F N W Y V D G V E V H -
TAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGT
6421
ATTACGGTTCTGTTTCGGCGCCCTCCTCGTCATGTTGTCGTGCATGGCACACCAGTCGCA
6480
b N A K T K P R E E Q Y N S T Y R V V S V -
EcoNI
CCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAA
6481
GGAGTGGCAGGACGTGGTCCTGACCGACTTACCGTTCCTCATGTTCACGTTCCAGAGGTT
6540
b L T V L H Q D W L N G K E Y K C K V S N -
CAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGA
6541
GTTTCGGGAGGGTCGGGGGTAGCTCTTTTGGTAGAGGTTTCGGTTTCCCGTCGGGGCTCT
6600
b K A L P A P I E K T I S K A K G Q P R E -
SmaI
BsrGI
BmaI
SexAI
ACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCT
6601
TGGTGTCCACATGTGGGACGGGGGTAGGGCCCTACTCGACTGGTTCTTGGTCCAGTCGGA
6660
b P Q V Y T L P P S R D E L T K N Q V S L -
GACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGG
6661
CTGGACGGACCAGTTTCCGAAGATAGGGTCGCTGTAGCGGCACCTCACCCTCTCGTTACC
6720
b T C L V K G F Y P S D I A V E W E S N G -
GCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTT
6721
CGTCGGCCTCTTGTTGATGTTCTGGTGCGGAGGGCACGACCTGAGGCTGCCGAGGAAGAA
6780

FIG. 5M

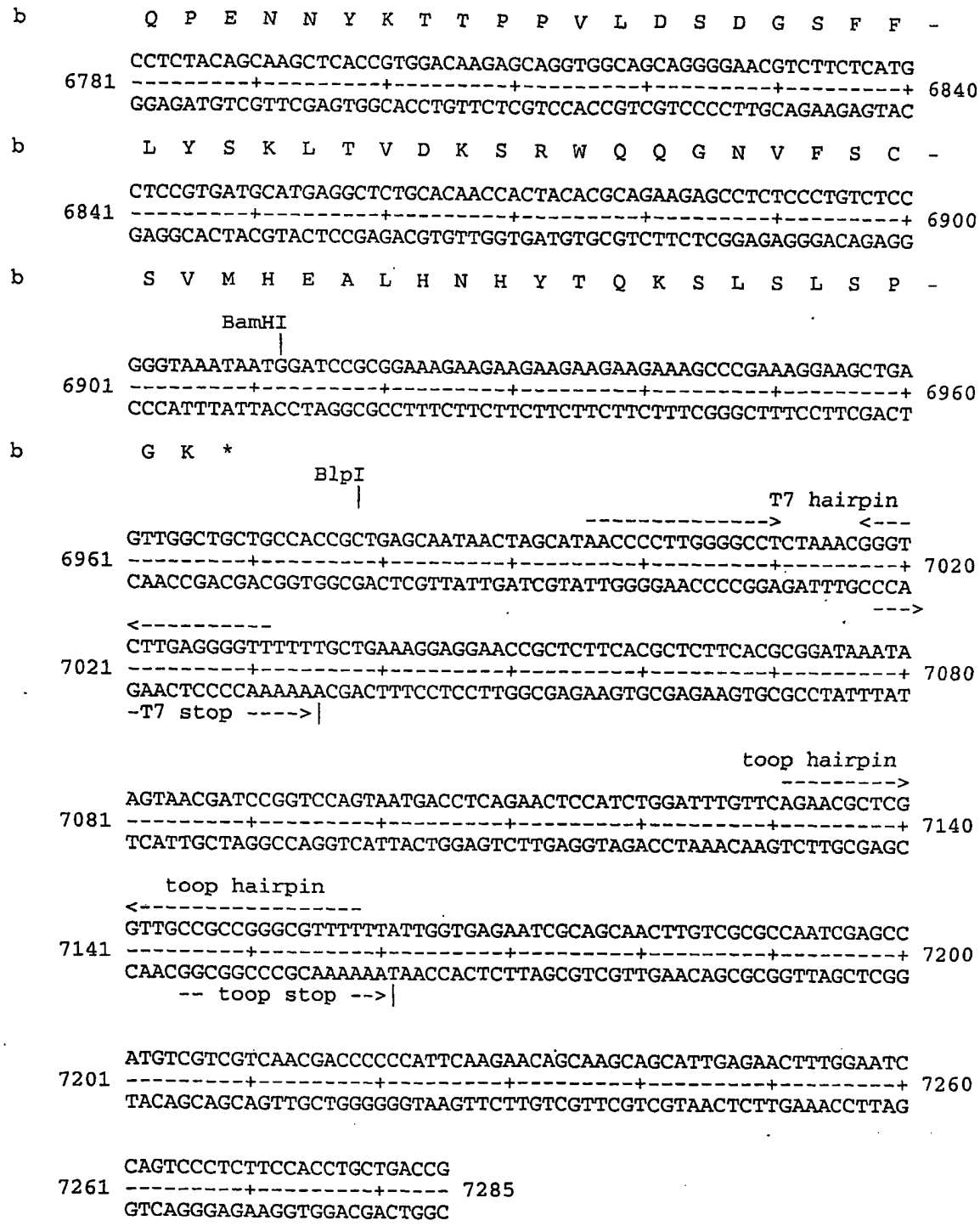

b Q P E N N Y K T T P P V L D S D G S F F -
CCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATG
6781 ---------+---------+---------+---------+---------+---------+ 6840
GGAGATGTCGTTCGAGTGGCACCTGTTCTCGTCCACCGTCGTCCCCTTGCAGAAGAGTAC
b L Y S K L T V D K S R W Q Q G N V F S C -
CTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCC
6841 ---------+---------+---------+---------+---------+---------+ 6900
GAGGCACTACGTACTCCGAGACGTGTTGGTGATGTGCGTCTTCTCGGAGAGGGACAGAGG
b S V M H E A L H N H Y T Q K S L S L S P -
BamHI
GGGTAAATAATGGATCCGCGGAAAGAAGAAGAAGAAGAAAGCCCGAAAGGAAGCTGA
6901 ---------+---------+---------+---------+---------+---------+ 6960
CCCATTTATTACCTAGGCGCCTTTCTTCTTCTTCTTCTTTCGGGCTTTCCTTCGACT
b G K *
BlpI
T7 hairpin
GTTGGCTGCTGCCACCGCTGAGCAATAACTAGCATAACCCCTTGGGGCCTCTAAACGGGT
6961 ---------+---------+---------+---------+---------+---------+ 7020
CAACCGACGACGGTGGCGACTCGTTATTGATCGTATTGGGGAACCCCGGAGATTTGCCCA
<----------
CTTGAGGGGTTTTTTGCTGAAAGGAGGAACCGCTCTTCACGCTCTTCACGCGGATAAATA
7021 ---------+---------+---------+---------+---------+---------+ 7080
GAACTCCCCAAAAAACGACTTTCCTCCTTGGCGAGAAGTGCGAGAAGTGCGCCTATTTAT
-T7 stop ---->|
toop hairpin
AGTAACGATCCGGTCCAGTAATGACCTCAGAACTCCATCTGGATTTGTTCAGAACGCTCG
7081 ---------+---------+---------+---------+---------+---------+ 7140
TCATTGCTAGGCCAGGTCATTACTGGAGTCTTGAGGTAGACCTAAACAAGTCTTGCGAGC
toop hairpin
<----------
GTTGCCGCCGGGCGTTTTTTATTGGTGAGAATCGCAGCAACTTGTCGCGCCAATCGAGCC
7141 ---------+---------+---------+---------+---------+---------+ 7200
CAACGGCGGCCCGCAAAAAATAACCACTCTTAGCGTCGTTGAACAGCGCGGTTAGCTCGG
-- toop stop -->|
ATGTCGTCGTCAACGACCCCCCATTCAAGAACAGCAAGCAGCATTGAGAACTTTGGAATC
7201 ---------+---------+---------+---------+---------+---------+ 7260
TACAGCAGCAGTTGCTGGGGGGTAAGTTCTTGTCGTTCGTCGTAACTCTTGAAACCTTAG
CAGTCCCTCTTCCACCTGCTGACCG
7261 ---------+---------+----- 7285
GTCAGGGAGAAGGTGGACGACTGGC

FIG. 6A

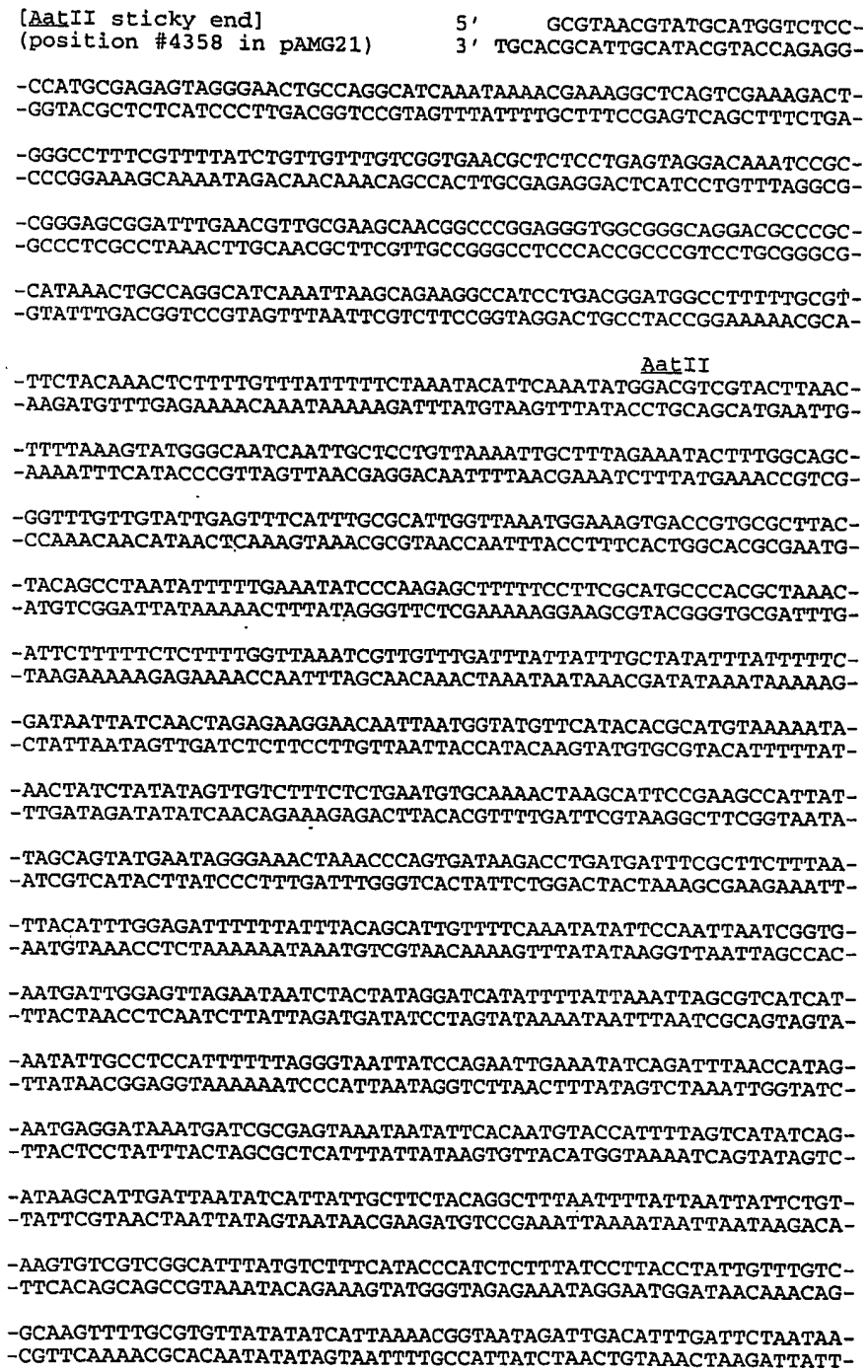

[AatII sticky end]
(position #4358 in pAMG21)
5' GCGTAACGTATGCATGGTCTCC-
3' TGCACGCATTGCATACGTACCAGAGG-
-CCATGCGAGAGTAGGGAACTGCCAGGCATCAAATAAAACGAAAGGCTCAGTCGAAAGACT-
-GGTACGCTCTCATCCCTTGACGGTCCGTAGTTTATTTTGCTTTCCGAGTCAGCTTTCTGA-
-GGGCCTTTCGTTTTATCTGTTGTTTGTCGGTGAACGCTCTCCTGAGTAGGACAAATCCGC-
-CCCGGAAAGCAAAATAGACAACAAACAGCCACTTGCGAGAGGACTCATCCTGTTTAGGCG-
-CGGGAGCGGATTTGAACGTTGCGAAGCAACGGCCCGGAGGGTGGCGGGCAGGACGCCCGC-
-GCCCTCGCCTAAACTTGCAACGCTTCGTTGCCGGGCCTCCCACCGCCCGTCCTGCGGGCG-
-CATAAACTGCCAGGCATCAAATTAAGCAGAAGGCCATCCTGACGGATGGCCTTTTTGCGT-
-GTATTTGACGGTCCGTAGTTTAATTCGTCTTCCGGTAGGACTGCCTACCGGAAAAACGCA-
AatII
-TTCTACAAACTCTTTTGTTTATTTTTCTAAATACATTCAAATATGGACGTCGTACTTAAC-
-AAGATGTTTGAGAAAACAAATAAAAAGATTTATGTAAGTTTATACCTGCAGCATGAATTG-
-TTTTAAAGTATGGGCAATCAATTGCTCCTGTTAAAATTGCTTTAGAAATACTTTGGCAGC-
-AAAATTTCATACCCGTTAGTTAACGAGGACAATTTTAACGAAATCTTTATGAAACCGTCG-
-GGTTTGTTGTATTGAGTTTCATTTGCGCATTGGTTAAATGGAAAGTGACCGTGCGCTTAC-
-CCAAACAACATAACTCAAAGTAAACGCGTAACCAATTTACCTTTCACTGGCACGCGAATG-
-TACAGCCTAATATTTTTGAAATATCCCAAGAGCTTTTTCCTTCGCATGCCCACGCTAAAC-
-ATGTCGGATTATAAAAACTTTATAGGGTTCTCGAAAAAGGAAGCGTACGGGTGCGATTTG-
-ATTCTTTTTCTCTTTTGGTTAAATCGTTGTTTGATTTATTATTTGCTATATTTATTTTTC-
-TAAGAAAAAGAGAAAACCAATTTAGCAACAAACTAAATAATAAACGATATAAATAAAAAG-
-GATAATTATCAACTAGAGAAGGAACAATTAATGGTATGTTCATACACGCATGTAAAAATA-
-CTATTAATAGTTGATCTCTTCCTTGTTAATTACCATACAAGTATGTGCGTACATTTTTAT-
-AACTATCTATATAGTTGTCTTTCTCTGAATGTGCAAAACTAAGCATTCCGAAGCCATTAT-
-TTGATAGATATATCAACAGAAAGAGACTTACACGTTTTGATTCGTAAGGCTTCGGTAATA-
-TAGCAGTATGAATAGGGAAACTAAACCCAGTGATAAGACCTGATGATTTCGCTTCTTTAA-
-ATCGTCATACTTATCCCTTTGATTTGGGTCACTATTCTGGACTACTAAAGCGAAGAAATT-
-TTACATTTGGAGATTTTTTATTTACAGCATTGTTTTCAAATATATTCCAATTAATCGGTG-
-AATGTAAACCTCTAAAAAATAAATGTCGTAACAAAAGTTTATATAAGGTTAATTAGCCAC-
-AATGATTGGAGTTAGAATAATCTACTATAGGATCATATTTTATTAAATTAGCGTCATCAT-
-TTACTAACCTCAATCTTATTAGATGATATCCTAGTATAAAATAATTTAATCGCAGTAGTA-
-AATATTGCCTCCATTTTTTAGGGTAATTATCCAGAATTGAAATATCAGATTTAACCATAG-
-TTATAACGGAGGTAAAAAATCCCATTAATAGGTCTTAACTTTATAGTCTAAATTGGTATC-
-AATGAGGATAAATGATCGCGAGTAAATAATATTCACAATGTACCATTTTAGTCATATCAG-
-TTACTCCTATTTACTAGCGCTCATTTATTATAAGTGTTACATGGTAAAATCAGTATAGTC-
-ATAAGCATTGATTAATATCATTATTGCTTCTACAGGCTTTAATTTTATTAATTATTCTGT-
-TATTCGTAACTAATTATAGTAATAACGAAGATGTCCGAAATTAAAATAATTAATAAGACA-
-AAGTGTCGTCGGCATTTATGTCTTTCATACCCATCTCTTTATCCTTACCTATTGTTTGTC-
-TTCACAGCAGCCGTAAATACAGAAAGTATGGGTAGAGAAATAGGAATGGATAACAAACAG-
-GCAAGTTTTGCGTGTTATATATCATTAAAACGGTAATAGATTGACATTTGATTCTAATAA-
-CGTTCAAAACGCACAATATATAGTAATTTTGCCATTATCTAACTGTAAACTAAGATTATT-

FIG. 6B

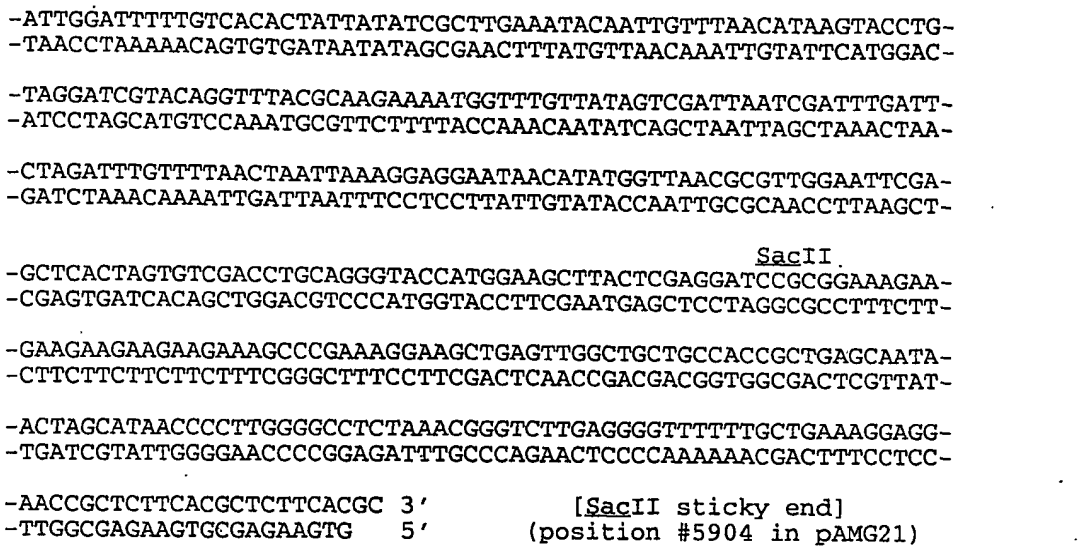

-ATTGGATTTTTGTCACACTATTATATCGCTTGAAATACAATTGTTTAACATAAGTACCTG-
-TAACCTAAAAACAGTGTGATAATATAGCGAACTTTATGTTAACAAATTGTATTCATGGAC-
-TAGGATCGTACAGGTTTACGCAAGAAAATGGTTTGTTATAGTCGATTAATCGATTTGATT-
-ATCCTAGCATGTCCAAATGCGTTCTTTTACCAAACAATATCAGCTAATTAGCTAAACTAA-
-CTAGATTTGTTTTAACTAATTAAAGGAGGAATAACATATGGTTAACGCGTTGGAATTCGA-
-GATCTAAACAAAATTGATTAATTTCCTCCTTATTGTATACCAATTGCGCAACCTTAAGCT-
SacII
-GCTCACTAGTGTCGACCTGCAGGGTACCATGGAAGCTTACTCGAGGATCCGCGGAAAGAA-
-CGAGTGATCACAGCTGGACGTCCCATGGTACCTTCGAATGAGCTCCTAGGCGCCTTTCTT-
-GAAGAAGAAGAAGAAAGCCCGAAAGGAAGCTGAGTTGGCTGCTGCCACCGCTGAGCAATA-
-CTTCTTCTTCTTCTTTCGGGCTTTCCTTCGACTCAACCGACGACGGTGGCGACTCGTTAT-
-ACTAGCATAACCCCTTGGGGCCTCTAAACGGGTCTTGAGGGGTTTTTTGCTGAAAGGAGG-
-TGATCGTATTGGGGAACCCCGGAGATTTGCCCAGAACTCCCCAAAAAACGACTTTCCTCC-
-AACCGCTCTTCACGCTCTTCACGC 3'
-TTGGCGAGAAGTGCGAGAAGTG 5'
[SacII sticky end]
(position #5904 in pAMG21)

FIG. 7

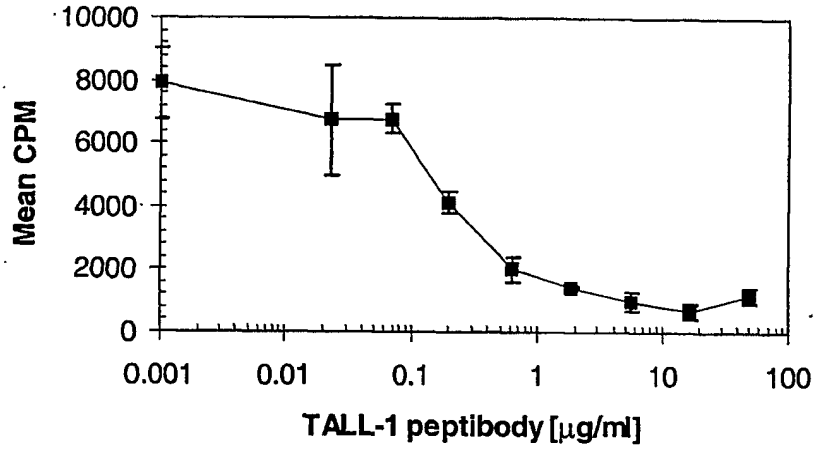

10000
8000
6000
4000
2000
0
Mean CPM
0.001
0.01
0.1
1
10
100
TALL-1 peptibody [μg/ml]

FIG. 8

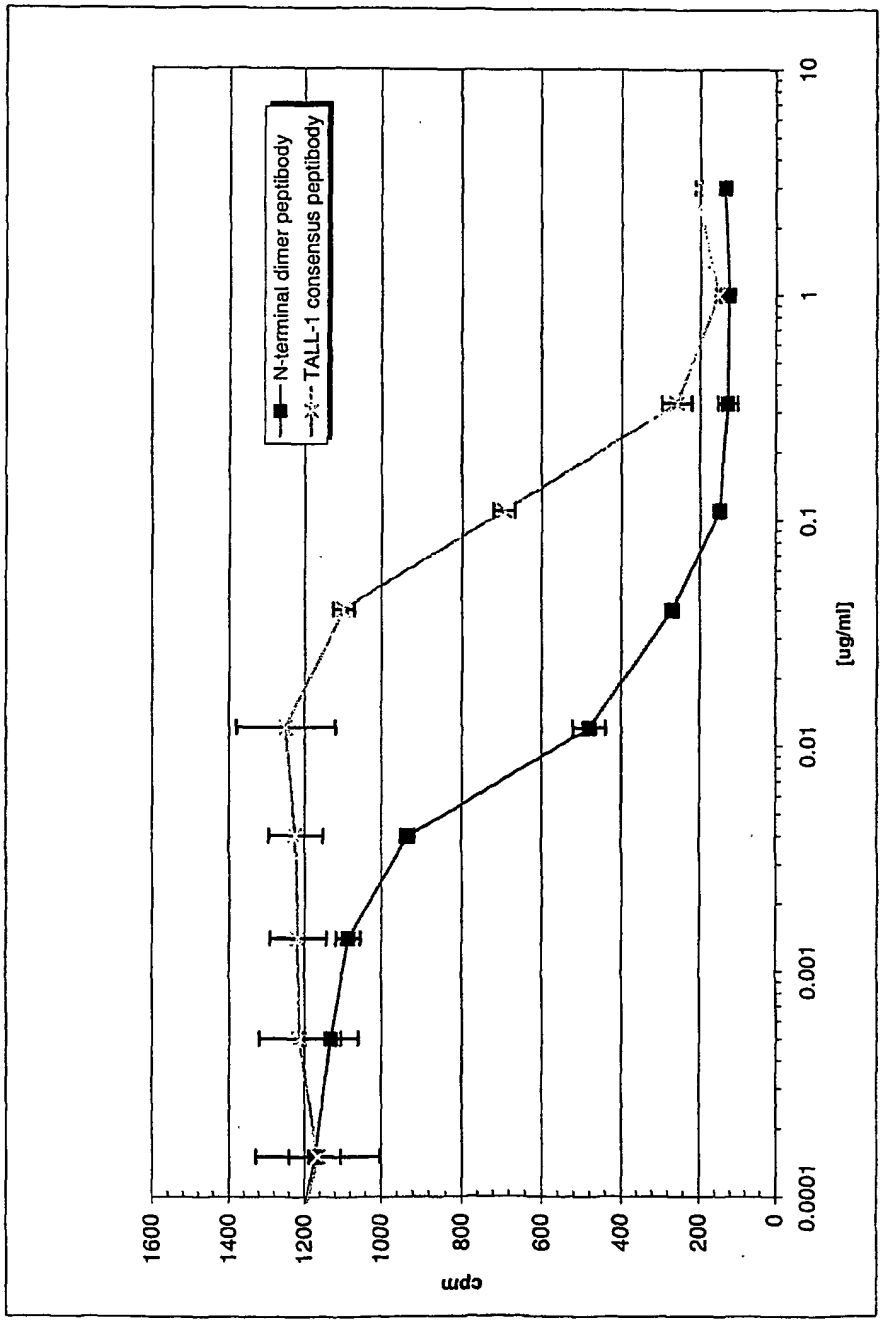

N-terminal dimer peptibody
TALL-1 consensus peptibody
cpm
1600
1400
1200
1000
800
600
400
200
0
0.0001
0.001
0.01
0.1
1
10
[ug/ml]

FIG. 9

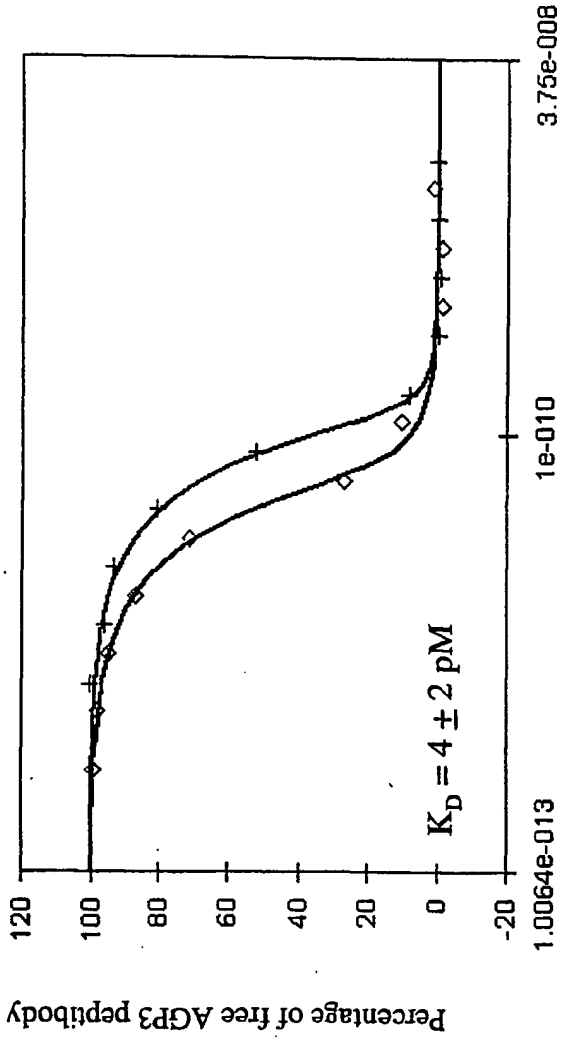

Percentage of free AGP3 peptibody
120
100
80
60
40
20
0
-20
1.0064e-013
1e-010
3.75e-008
[hAGP3] M
$K_D = 4 \pm 2$ pM
40 pM AGP3 peptibody
100 pM AGP3 peptibody

FIG. 10A

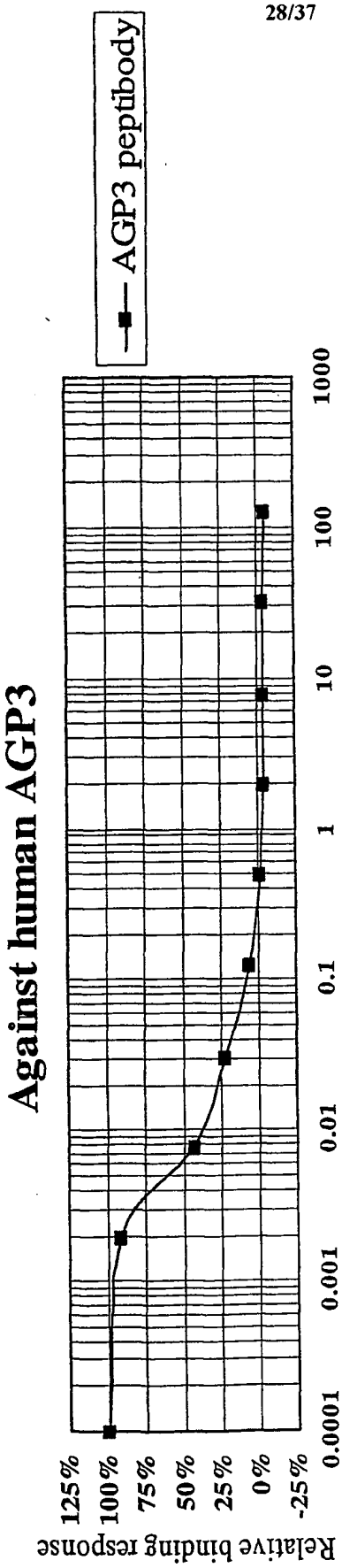

Against human AGP3
AGP3 peptibody
Relative binding response
125%
100%
75%
50%
25%
0%
-25%
0.0001
0.001
0.01
0.1
1
10
100
1000

FIG. 10B

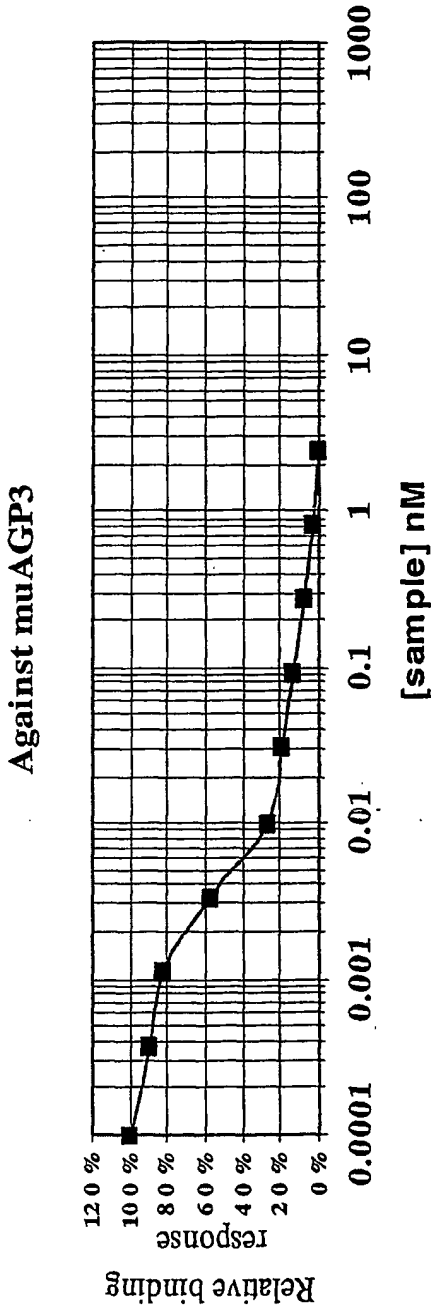

Against muAGP3
Relative binding response
120 %
100 %
80 %
60 %
40 %
20 %
0 %
0.0001
0.001
0.01
0.1
1
10
100
1000
[sample] nM

FIG. 11A

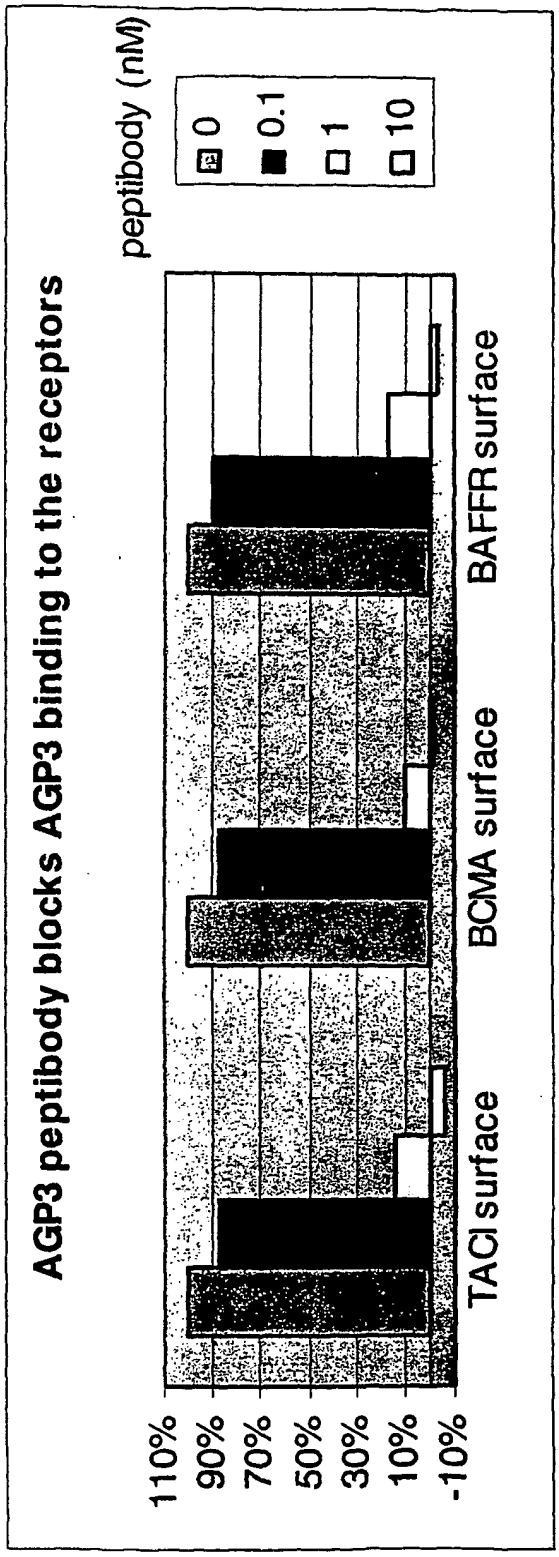

AGP3 peptibody blocks AGP3 binding to the receptors
peptibody (nM)
0
0.1
1
10
110%
90%
70%
50%
30%
10%
-10%
TACI surface
BCMA surface
BAFFR surface

FIG. 11B

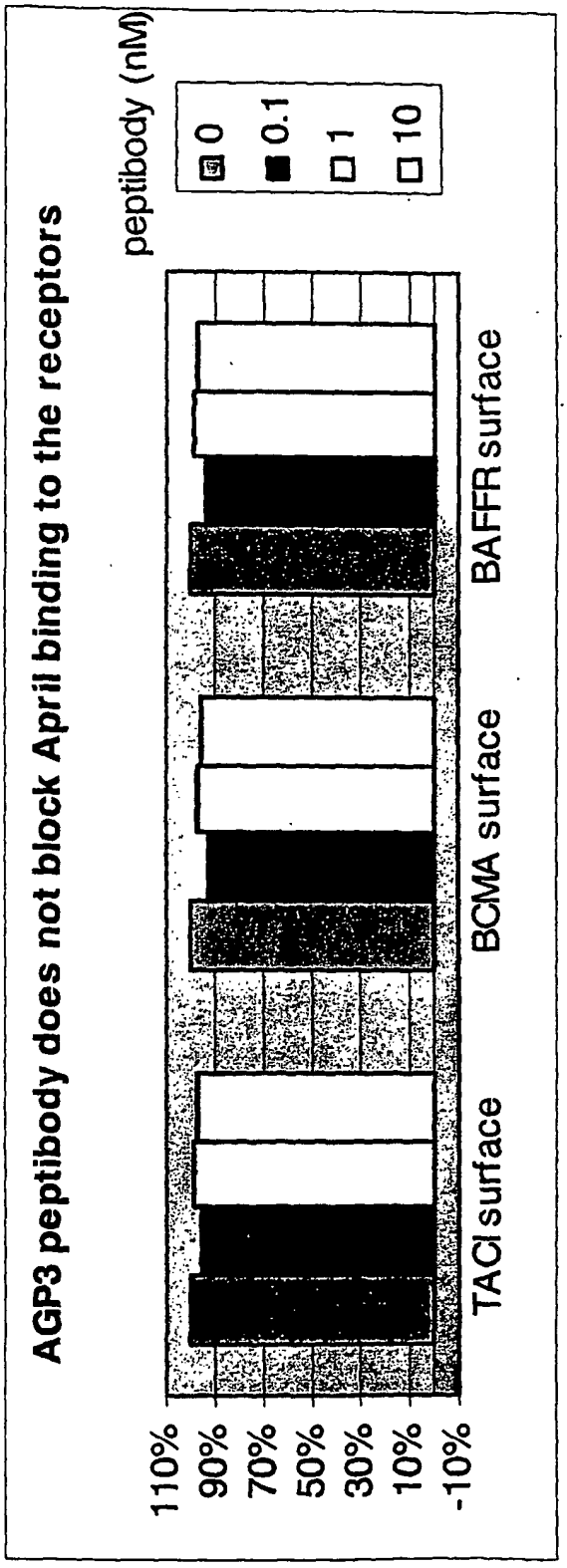

AGP3 peptibody does not block April binding to the receptors
peptibody (nM)
0
0.1
1
10
110%
90%
70%
50%
30%
10%
-10%
TACI surface
BCMA surface
BAFFR surface

FIG. 12A

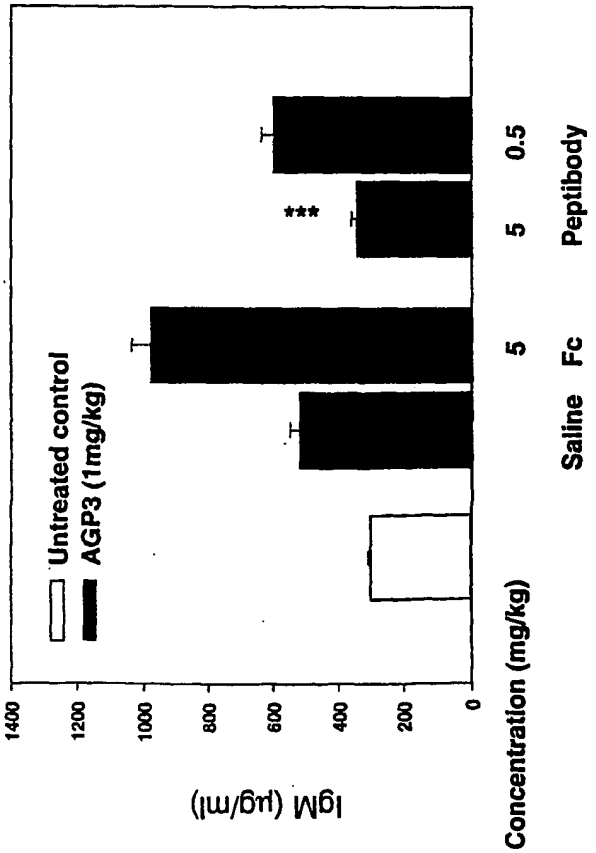


FIG. 12B

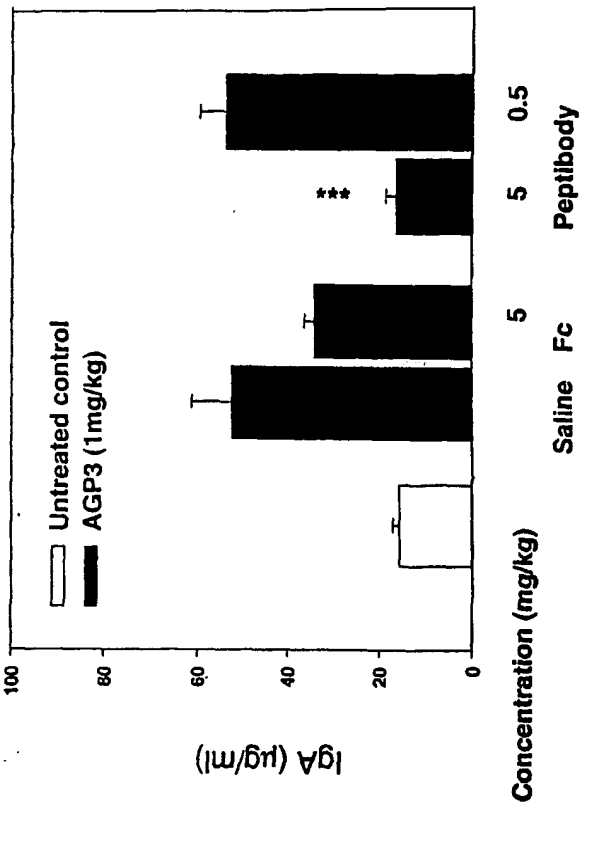
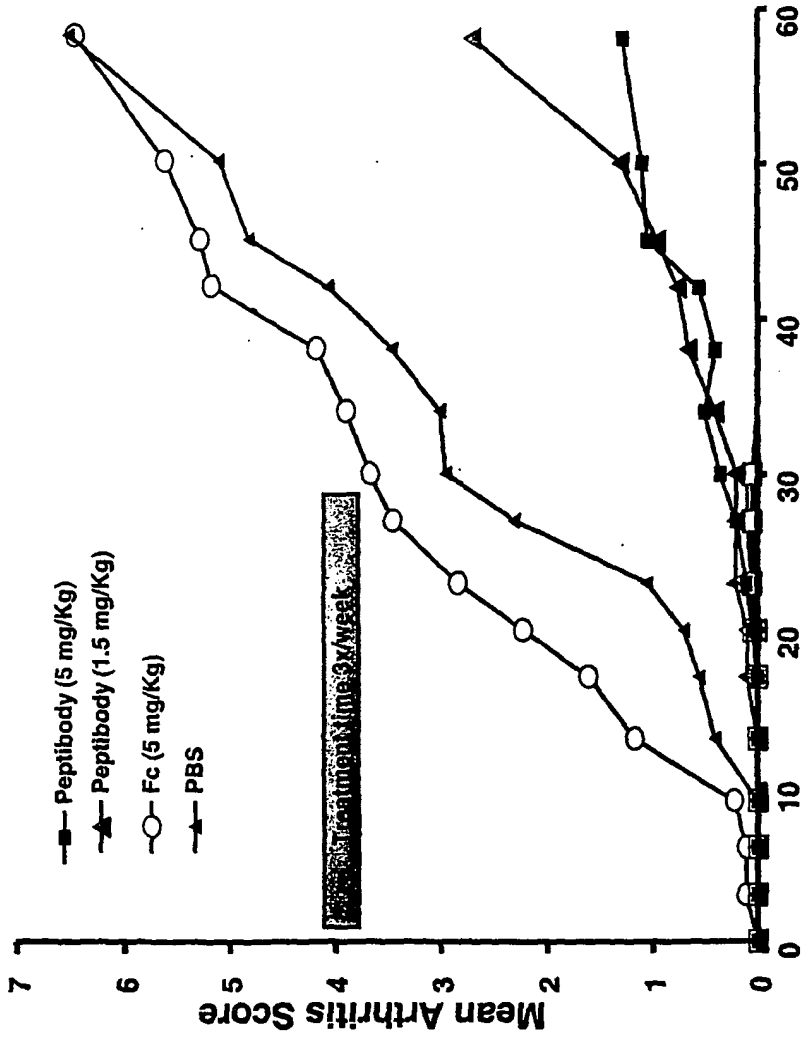


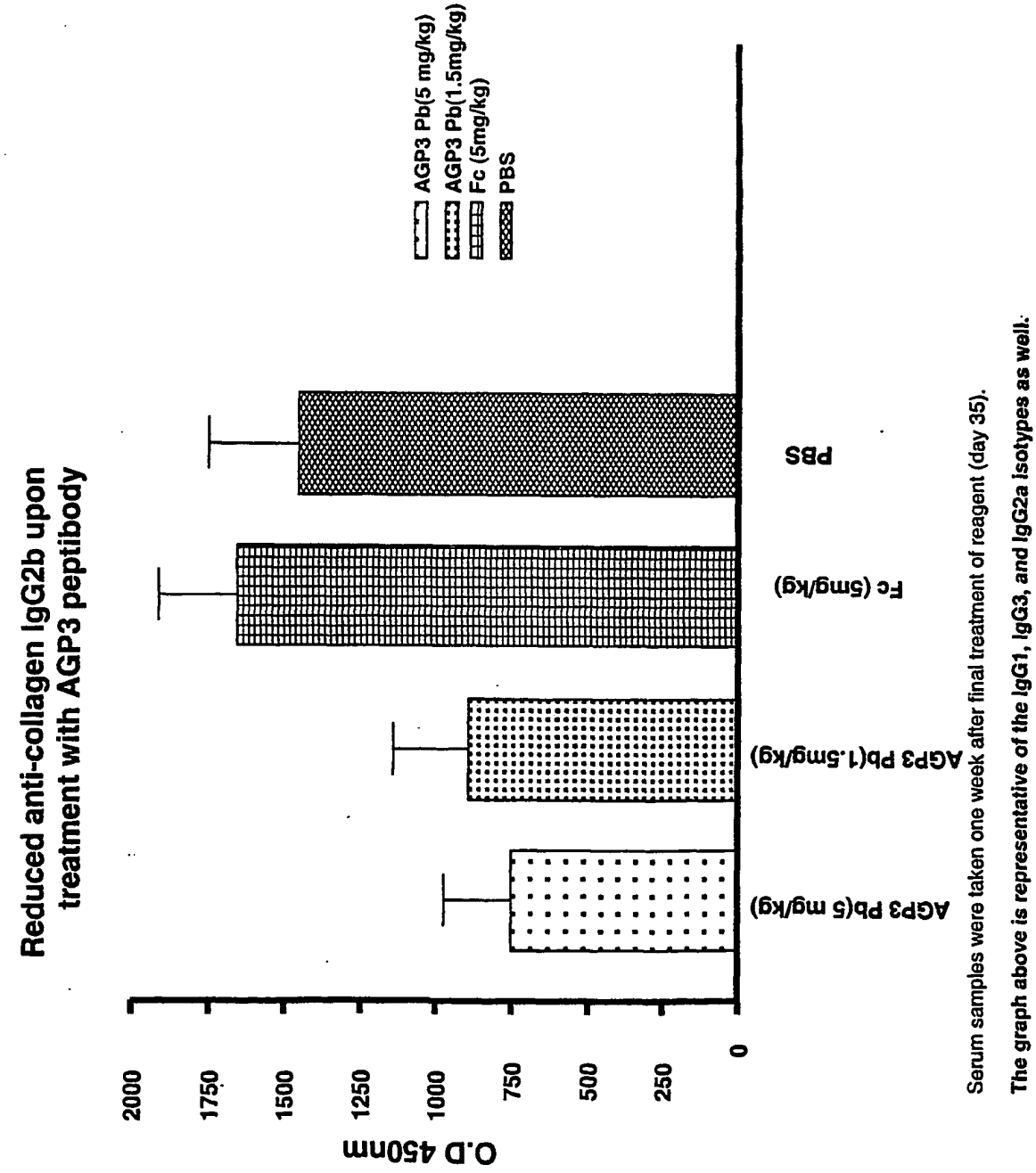
FIG. 13



Time-to-Disease	Pb (5mg/Kg)	Pb (1.5mg/Kg)
P-value vs PBS	<0.0001	0.0001
P-value vs Fc	<0.0001	0.0004

Note: p-value based on log-rank test

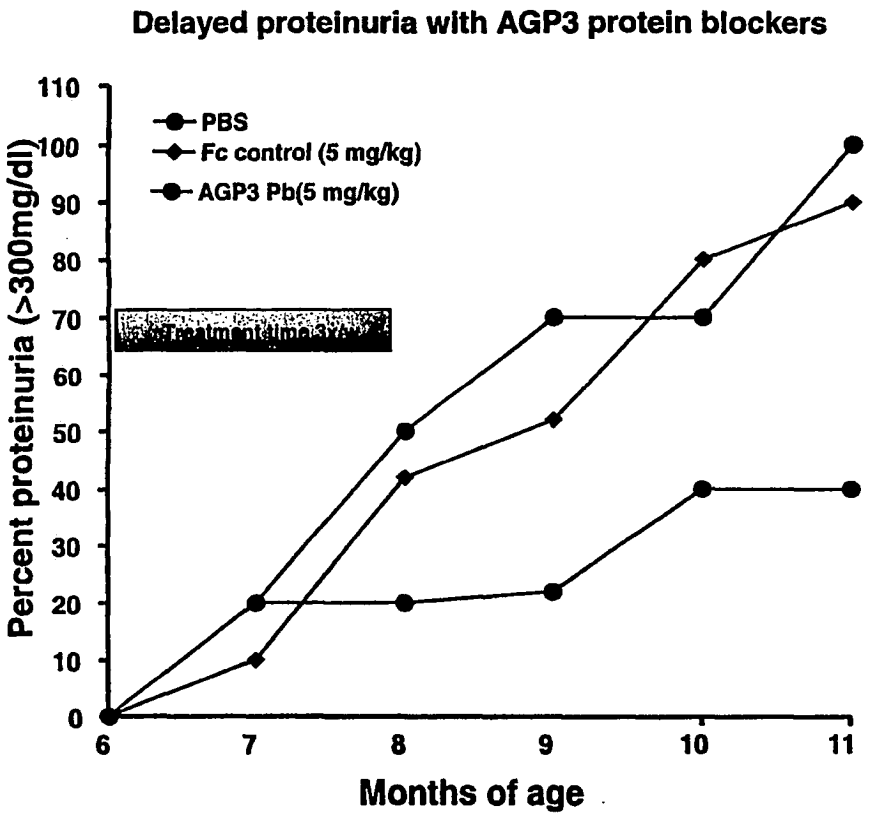
FIG. 14



Serum samples were taken one week after final treatment of reagent (day 35).

The graph above is representative of the IgG1, IgG3, and IgG2a isotypes as well.

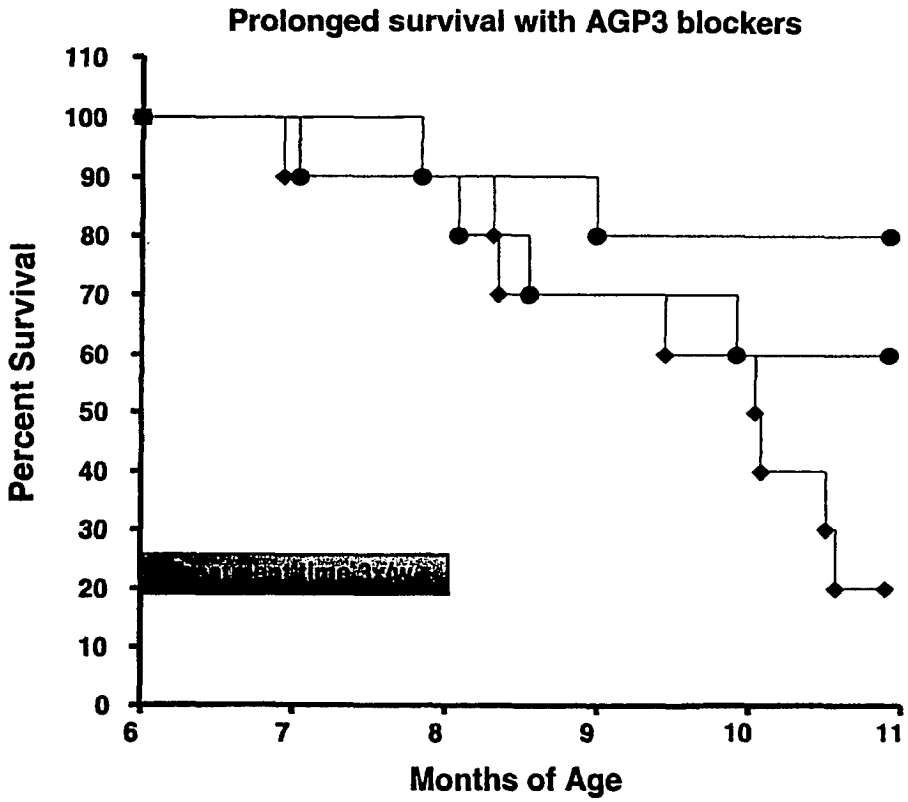
Fig. 15A



Proteinuria Incidence	Pb
p-value vs PBS	0.0108
P-vs Fc	0.0573

P-value based Fisher's Exact test

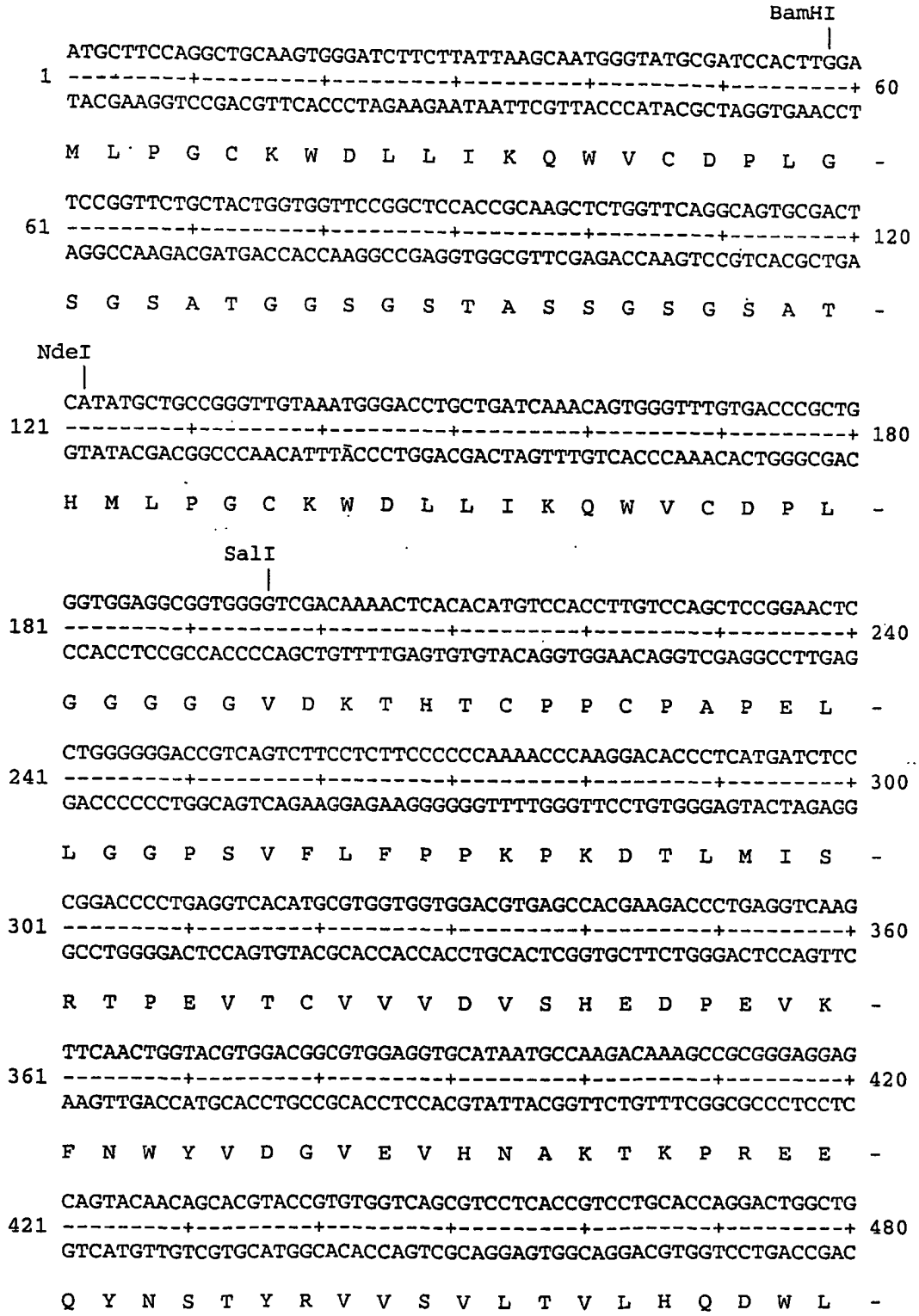
Fig. 15B



Time-to-Death	Pb
p-value vs PBS	0.3685
p-value vs Fc	0.0159

P-value based log-rank test

FIG. 16A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ATGCTTCCAGGCTGCAAGTGGGATCTTCTTATTAAGCAATGGGTATGCGATCCACTTGGA
1
60
TACGAAGGTCCGACGTTCACCCTAGAAGAATAATTCGTTACCCATACGCTAGGTGAACCT
M L P G C K W D L L I K Q W V C D P L G -
TCCGGTTCTGCTACTGGTGGTTCCGGCTCCACCGCAAGCTCTGGTTCAGGCAGTGCGACT
61
120
AGGCCAAGACGATGACCACCAAGGCCGAGGTGGCGTTCGAGACCAAGTCCGTCACGCTGA
S G S A T G G S G S T A S S G S G S A T -
NdeI
CATATGCTGCCGGGTTGTAAATGGGACCTGCTGATCAAACAGTGGGTTTGTGACCCGCTG
121
180
GTATACGACGGCCCAACATTTACCCTGGACGACTAGTTTGTCACCCAAACACTGGGCGAC
H M L P G C K W D L L I K Q W V C D P L -
SalI
GGTGGAGGCGGTGGGGTCGACAAAACTCACACATGTCCACCTTGTCCAGCTCCGGAACTC
181
240
CCACCTCCGCCACCCCAGCTGTTTTGAGTGTGTACAGGTGGAACAGGTCGAGGCCTTGAG
G G G G G V D K T H T C P P C P A P E L -
CTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCC
241
300
GACCCCCCTGGCAGTCAGAAGGAGAAGGGGGGTTTTGGGTTCCTGTGGGAGTACTAGAGG
L G G P S V F L F P P K P K D T L M I S -
CGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAG
301
360
GCCTGGGGACTCCAGTGTACGCACCACCACCTGCACTCGGTGCTTCTGGGACTCCAGTTC
R T P E V T C V V V D V S H E D P E V K -
TTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAG
361
420
AAGTTGACCATGCACCTGCCGCACCTCCACGTATTACGGTTCTGTTTCGGCGCCCTCCTC
F N W Y V D G V E V H N A K T K P R E E -
CAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTG
421
480
GTCATGTTGTCGTGCATGGCACACCAGTCGCAGGAGTGGCAGGACGTGGTCCTGACCGAC
Q Y N S T Y R V V S V L T V L H Q D W L -

FIG. 16B

```
    AATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAA
481 ---------+---------+---------+---------+---------+---------+ 540
    TTACCGTTCCTCATGTTCACGTTCCAGAGGTTGTTTCGGGAGGGTCGGGGGTAGCTCTTT

    N  G  K  E  Y  K  C  K  V  S  N  K  A  L  P  A  P  I  E  K  -

    ACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCC
541 ---------+---------+---------+---------+---------+---------+ 600
    TGGTAGAGGTTTCGGTTTCCCGTCGGGGCTCTTGGTGTCCACATGTGGGACGGGGGTAGG

    T  I  S  K  A  K  G  Q  P  R  E  P  Q  V  Y  T  L  P  P  S  -

    CGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCC
601 ---------+---------+---------+---------+---------+---------+ 660
    GCCCTACTCGACTGGTTCTTGGTCCAGTCGGACTGGACGGACCAGTTTCCGAAGATAGGG

    R  D  E  L  T  K  N  Q  V  S  L  T  C  L  V  K  G  F  Y  P  -

    AGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACG
661 ---------+---------+---------+---------+---------+---------+ 720
    TCGCTGTAGCGGCACCTCACCCTCTCGTTACCCGTCGGCCTCTTGTTGATGTTCTGGTGC

    S  D  I  A  V  E  W  E  S  N  G  Q  P  E  N  N  Y  K  T  T  -

    CCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAG
721 ---------+---------+---------+---------+---------+---------+ 780
    GGAGGGCACGACCTGAGGCTGCCGAGGAAGAAGGAGATGTCGTTCGAGTGGCACCTGTTC

    P  P  V  L  D  S  D  G  S  F  F  L  Y  S  K  L  T  V  D  K  -

    AGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAAC
781 ---------+---------+---------+---------+---------+---------+ 840
    TCGTCCACCGTCGTCCCCTTGCAGAAGAGTACGAGGCACTACGTACTCCGAGACGTGTTG

    S  R  W  Q  Q  G  N  V  F  S  C  S  V  M  H  E  A  L  H  N  -

    CACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATAA
841 ---------+---------+---------+---------+-- 882
    GTGATGTGCGTCTTCTCGGAGAGGGACAGAGGCCCATTTATT

    H  Y  T  Q  K  S  L  S  L  S  P  G  K  *  -
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A-743 PCT.ST25.txt
SEQUENCE LISTING

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<141> 2002-05-13

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<151> 2001-05-11

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<170> PatentIn version 3.1

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Met Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
1               5                  10                  15

ggg gga ccg tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc       96
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
            20                  25                  30

atg atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc      144
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
        35                  40                  45

cac gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag      192
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
    50                  55                  60

gtg cat aat gcc aag aca aag ccg cgg gag gag cag tac aac agc acg      240
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
65                  70                  75                  80

tac cgt gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat      288
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
                85                  90                  95

ggc aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc      336
Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
            100                 105                 110

atc gag aaa acc atc tcc aaa gcc aaa ggg cag ccc cga gaa cca cag      384
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
        115                 120                 125

gtg tac acc ctg ccc cca tcc cgg gat gag ctg acc aag aac cag gtc      432
Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
    130                 135                 140

agc ctg acc tgc ctg gtc aaa ggc ttc tat ccc agc gac atc gcc gtg      480
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
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145 150 155 160

gag tgg gag agc aat ggg cag ccg gag aac aac tac aag acc acg cct 528
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
165 170 175

ccc gtg ctg gac tcc gac ggc tcc ttc ttc ctc tac agc aag ctc acc 576
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
180 185 190

gtg gac aag agc agg tgg cag cag ggg aac gtc ttc tca tgc tcc gtg 624
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
195 200 205

atg cat gag gct ctg cac aac cac tac acg cag aag agc ctc tcc ctg 672
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His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
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Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
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Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
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Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
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Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
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<221> misc_feature
<223> Xaa (Pos1,2,3,15,16,17) are each independently absent or amino acid residues;
Xaa (Pos5,6,7,9,13) are each independently amino acid residues.

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35 40 45

Thr Thr Gly Thr Cys Cys Ala Ala Cys Cys Cys Cys Gly Gly Ala Ala
50 55 60

Ala Cys Gly Gly Gly Ala Ala Ala Ala Ala Gly Cys Ala Ala Gly Thr
65 70 75 80

```
Thr Thr Thr Cys Cys Cys Cys Gly Cys Thr Cys Cys Cys Gly Gly Cys
                85                  90                  95

Gly Thr Thr Thr Cys Ala Ala Thr Ala Ala Cys Thr Gly Ala Ala Ala
            100                 105                 110

Ala Cys Cys Ala Thr Ala Cys Thr Ala Thr Thr Thr Cys Ala Cys Ala
        115                 120                 125

Gly Thr Thr Thr Ala Ala Ala Thr Cys Ala Cys Ala Thr Thr Ala Ala
    130                 135                 140

Ala Cys Gly Ala Cys Ala Gly Thr Ala Ala Thr Cys Cys Cys Cys Gly
145                 150                 155                 160

Thr Thr Gly Ala Thr Thr Thr Gly Thr Gly Cys Gly Cys Cys Ala Ala
                165                 170                 175

Cys Ala Cys Ala Gly Ala Thr Cys Thr Thr Cys Gly Thr Cys Ala Cys
            180                 185                 190

Ala Ala Thr Thr Cys Thr Cys Ala Ala Gly Thr Cys Gly Cys Thr Gly
        195                 200                 205

Ala Thr Thr Thr Cys Ala Ala Ala Ala Ala Ala Cys Thr Gly Thr Ala
    210                 215                 220

Gly Thr Ala Thr Cys Cys Thr Cys Thr Gly Cys Gly Ala Ala Ala Cys
225                 230                 235                 240

Gly Ala Thr Cys Cys Cys Thr Gly Thr Thr Thr Gly Ala Gly Thr Ala
                245                 250                 255

Thr Thr Gly Ala Gly Gly Ala Gly Gly Cys Gly Ala Gly Ala Thr Gly
            260                 265                 270

Thr Cys Gly Cys Ala Gly Ala Cys Ala Gly Ala Ala Ala Ala Thr Gly
        275                 280                 285

Cys Ala Gly Thr Gly Ala Cys Thr Thr Cys Cys Thr Cys Ala Thr Thr
    290                 295                 300

Gly Ala Gly Thr Cys Ala Ala Ala Ala Gly Cys Gly Gly Thr Thr Thr
305                 310                 315                 320

Gly Thr Gly Cys Gly Cys Ala Gly Ala Gly Gly Thr Ala Ala Gly Cys
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Cys Thr Ala Thr Gly Ala Cys Thr Gly Ala Cys Thr Cys Thr Gly Ala
            340                 345                 350
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Gly Ala Ala Ala Cys Ala Ala Ala Thr Gly Gly Cys Cys Gly Thr Thr
        355                 360                 365

Gly Thr Thr Gly Cys Ala Ala Gly Ala Ala Ala Ala Cys Gly Thr Cys
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Thr Thr Ala Cys Ala Cys Ala Cys Ala Ala Ala Gly Ala Gly Ala Thr
385                 390                 395                 400

Ala Ala Ala Ala Gly Thr Thr Thr Thr Thr Gly Thr Cys Ala Ala Ala
                405                 410                 415

Ala Ala Thr Cys Cys Thr Cys Thr Gly Ala Ala Gly Gly Ala Thr Cys
            420                 425                 430

Thr Cys Ala Thr Gly Gly Thr Thr Gly Ala Gly Thr Ala Cys Thr Gly
        435                 440                 445

Cys Gly Ala Gly Ala Gly Ala Gly Ala Gly Gly Gly Gly Ala Thr Ala
    450                 455                 460

Ala Cys Ala Cys Ala Gly Gly Cys Thr Cys Ala Gly Thr Thr Cys Gly
465                 470                 475                 480

Thr Thr Gly Ala Gly Ala Ala Ala Ala Thr Cys Ala Thr Cys Ala Ala
                485                 490                 495

Ala Gly Ala Thr Gly Ala Ala Cys Thr Gly Cys Ala Ala Ala Gly Ala
            500                 505                 510

Cys Thr Gly Gly Ala Thr Ala Thr Ala Cys Thr Ala Ala Ala Gly Thr
        515                 520                 525

Ala Ala Ala Gly Ala Cys Thr Thr Thr Ala Cys Thr Thr Thr Gly Thr
    530                 535                 540

Gly Gly Cys Gly Thr Ala Gly Cys Ala Thr Gly Cys Thr Ala Gly Ala
545                 550                 555                 560

Thr Thr Ala Cys Thr Gly Ala Thr Cys Gly Thr Thr Thr Ala Ala Gly
                565                 570                 575

Gly Ala Ala Thr Thr Thr Thr Gly Thr Gly Gly Cys Thr Gly Gly Cys
            580                 585                 590

Cys Ala Cys Gly Cys Cys Gly Thr Ala Ala Gly Gly Thr Gly Gly Cys
        595                 600                 605

Ala Ala Gly Gly Ala Ala Cys Thr Gly Gly Thr Thr Cys Thr Gly Ala
    610                 615                 620
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Cys Cys Ala Gly Ala Ala Ala Ala Gly Cys Ala Ala Ala Ala Ala Cys
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Cys Cys Cys Gly Ala Thr Ala Ala Thr Cys Thr Thr Cys Thr Thr Cys
            660                 665                 670

Ala Ala Cys Thr Thr Thr Thr Gly Cys Gly Ala Gly Thr Ala Cys Gly
        675                 680                 685

Ala Ala Ala Ala Gly Ala Thr Thr Ala Cys Cys Gly Gly Gly Gly Cys
    690                 695                 700

Cys Cys Ala Cys Thr Thr Ala Ala Ala Cys Cys Gly Thr Ala Thr Ala
705                 710                 715                 720

Gly Cys Cys Ala Ala Cys Ala Ala Thr Thr Cys Ala Gly Cys Thr Ala
                725                 730                 735

Thr Gly Cys Gly Gly Gly Gly Ala Gly Thr Ala Thr Ala Gly Thr Thr
            740                 745                 750

Ala Thr Ala Thr Gly Cys Cys Cys Gly Gly Ala Ala Ala Ala Gly Thr
        755                 760                 765

Thr Cys Ala Ala Gly Ala Cys Thr Thr Cys Thr Thr Thr Cys Thr Gly
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Thr Gly Cys Thr Cys Gly Cys Thr Cys Cys Thr Thr Cys Thr Gly Cys
785                 790                 795                 800

Gly Cys Ala Thr Thr Gly Thr Ala Ala Gly Thr Gly Cys Ala Gly Gly
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Ala Thr Gly Gly Thr Gly Thr Gly Ala Cys Thr Gly Ala Thr Cys Thr
            820                 825                 830

Thr Cys Ala Cys Cys Ala Ala Ala Cys Gly Thr Ala Thr Thr Ala Cys
        835                 840                 845

Cys Gly Cys Cys Ala Gly Gly Thr Ala Ala Ala Gly Ala Ala Cys Cys
    850                 855                 860

Cys Gly Ala Ala Thr Cys Cys Gly Gly Thr Gly Thr Thr Thr Ala Cys
865                 870                 875                 880

Ala Cys Cys Cys Cys Gly Thr Gly Ala Ala Gly Gly Thr Gly Cys Ala
                885                 890                 895
```

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Gly Gly Ala Ala Cys Gly Cys Thr Gly Ala Ala Gly Thr Thr Cys Thr
            900                 905                 910

Gly Cys Gly Ala Ala Ala Ala Ala Cys Thr Gly Ala Thr Gly Gly Ala
        915                 920                 925

Ala Ala Ala Gly Gly Cys Gly Gly Thr Gly Gly Gly Cys Thr Thr Cys
    930                 935                 940

Ala Cys Thr Thr Cys Cys Cys Gly Thr Thr Thr Thr Gly Ala Thr Thr
945                 950                 955                 960

Thr Cys Gly Cys Cys Ala Thr Thr Cys Ala Thr Gly Thr Gly Gly Cys
                965                 970                 975

Gly Cys Ala Cys Gly Cys Cys Cys Gly Thr Thr Cys Gly Cys Gly Thr
            980                 985                 990

Gly Ala Thr Cys Thr Gly Cys Gly  Thr Cys Gly Cys Cys  Gly Thr Ala
        995                 1000                1005

Thr Gly  Cys Cys Ala Cys Cys  Ala Gly Thr Gly Cys  Thr Gly Cys
    1010                1015                1020

Gly Thr  Cys Gly Thr Cys Gly  Gly Gly Cys Thr Ala  Thr Thr Gly
    1025                1030                1035

Ala Thr  Gly Cys Gly Cys Thr  Cys Thr Thr Gly Cys  Ala Gly Gly
    1040                1045                1050

Gly Gly  Cys Thr Gly Thr Gly  Thr Thr Thr Cys Cys  Ala Cys Thr
    1055                1060                1065

Ala Thr  Gly Ala Cys Cys Cys  Gly Cys Thr Gly Gly  Cys Cys Ala
    1070                1075                1080

Ala Cys  Cys Gly Cys Gly Thr  Cys Cys Ala Gly Thr  Gly Cys Thr
    1085                1090                1095

Cys Cys  Ala Thr Cys Ala Cys  Cys Ala Cys Gly Cys  Thr Gly Gly
    1100                1105                1110

Cys Cys  Ala Thr Thr Gly Ala  Gly Thr Gly Cys Gly  Gly Ala Cys
    1115                1120                1125

Thr Gly  Gly Cys Gly Ala Cys  Gly Gly Ala Gly Thr  Cys Thr Gly
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Cys Thr  Gly Cys Cys Gly Gly  Ala Ala Ala Ala Cys  Thr Cys Thr
    1145                1150                1155
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Cys Cys  Ala Thr Cys Ala Cys  Cys Cys Gly Thr Gly  Cys Cys Ala
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Thr Cys  Cys Thr Gly Thr Cys  Ala Gly Ala Gly Cys  Thr Gly Gly
    1190                 1195                 1200

Gly Ala  Cys Thr Gly Ala Thr  Thr Ala Cys Cys Thr  Ala Cys Cys
    1205                 1210                 1215

Ala Gly  Ala Cys Gly Gly Ala  Ala Thr Ala Thr Gly  Ala Cys Cys
    1220                 1225                 1230

Cys Gly  Cys Thr Thr Ala Thr  Cys Gly Gly Gly Thr  Gly Cys Thr
    1235                 1240                 1245

Ala Cys  Ala Thr Thr Cys Cys  Gly Ala Cys Cys Gly  Ala Thr Ala
    1250                 1255                 1260

Thr Cys  Ala Cys Gly Thr Thr  Cys Ala Cys Ala Thr  Cys Thr Gly
    1265                 1270                 1275

Cys Ala  Cys Thr Gly Thr Thr  Thr Gly Cys Thr Gly  Cys Cys Cys
    1280                 1285                 1290

Thr Cys  Gly Ala Thr Gly Thr  Ala Thr Cys Ala Gly  Ala Gly Gly
    1295                 1300                 1305

Ala Gly  Gly Cys Ala Gly Thr  Gly Gly Cys Cys Gly  Cys Cys Gly
    1310                 1315                 1320

Cys Gly  Cys Gly Cys Cys Gly  Cys Ala Gly Cys Cys  Gly Thr Gly
    1325                 1330                 1335

Thr Gly  Gly Thr Ala Thr Gly  Gly Gly Ala Ala Ala  Ala Cys Ala
    1340                 1345                 1350

Ala Ala  Cys Ala Ala Cys Gly  Cys Ala Ala Ala Ala  Ala Gly Cys
    1355                 1360                 1365

Ala Gly  Gly Gly Gly Cys Thr  Gly Gly Ala Thr Ala  Cys Cys Cys
    1370                 1375                 1380

Thr Gly  Gly Gly Cys Ala Thr  Gly Gly Ala Thr Gly  Ala Ala Cys
    1385                 1390                 1395

Thr Gly  Ala Thr Ala Gly Cys  Gly Ala Ala Ala Gly  Cys Cys Thr
    1400                 1405                 1410
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1445 1450 1455

Ala Gly Thr Cys Cys Cys Gly Thr Gly Gly Ala Ala Thr Ala Ala
1460 1465 1470

Ala Gly Cys Gly Thr Gly Cys Cys Cys Gly Thr Gly Cys Gly Cys
1475 1480 1485

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1490 1495 1500

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Thr Thr Gly Thr Cys Ala Cys Cys Cys Thr Gly Gly Thr Gly Ala
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1595 1600 1605

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1715 1720 1725

Cys Thr Gly Ala Ala Gly Cys Cys Cys Gly Ala Cys Ala Gly Cys
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Ala Cys Ala Ala Cys Cys Gly Thr Thr Cys Ala Thr Gly Thr Cys
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Gly Cys Ala Ala Thr Gly Thr Ala Thr Cys Thr Thr Thr Thr Ala
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1955 1960 1965

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1970 1975 1980

Thr Ala Ala Thr Thr Ala Cys Ala Thr Thr Cys Ala Thr Thr Thr
1985 1990 1995

Ala Ala Ala Ala Ala Gly Ala Ala Ala Ala Cys Cys Thr Ala Thr
2000 2005 2010

Thr Cys Ala Cys Thr Gly Cys Cys Thr Gly Thr Cys Cys Thr Thr
2015 2020 2025

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2855 2860 2865

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Gly Cys Cys Ala Ala Gly Cys Thr Cys Thr Thr Cys Ala Gly Cys
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Cys Ala Thr Thr Cys Ala Ala Ala Thr Ala Thr Gly Gly Ala Cys
4655 4660 4665

Gly Thr Cys Gly Thr Ala Cys Thr Thr Ala Ala Cys Thr Thr Thr
4670 4675 4680

Thr Ala Ala Ala Gly Thr Ala Thr Gly Gly Gly Cys Ala Ala Thr
4685 4690 4695

Cys Ala Ala Thr Thr Gly Cys Thr Cys Cys Thr Gly Thr Thr Ala
4700 4705 4710

Ala Ala Ala Thr Thr Gly Cys Thr Thr Thr Ala Gly Ala Ala Ala
4715 4720 4725

Thr Ala Cys Thr Thr Thr Gly Gly Cys Ala Gly Cys Gly Gly Thr
4730 4735 4740

Thr Thr Gly Thr Thr Gly Thr Ala Thr Thr Gly Ala Gly Thr Thr
4745 4750 4755

Thr Cys Ala Thr Thr Thr Gly Cys Gly Cys Ala Thr Thr Gly Gly
4760 4765 4770

Thr Thr Ala Ala Ala Thr Gly Gly Ala Ala Ala Gly Thr Gly Ala
4775 4780 4785

Cys Cys Gly Thr Gly Cys Gly Cys Thr Thr Ala Cys Thr Ala Cys
4790 4795 4800

Ala Gly Cys Cys Thr Ala Ala Thr Ala Thr Thr Thr Thr Thr Gly
4805 4810 4815

Ala Ala Ala Thr Ala Thr Cys Cys Cys Ala Ala Gly Ala Gly Cys
4820 4825 4830

Thr Thr Thr Thr Thr Cys Cys Thr Thr Cys Gly Cys Ala Thr Gly
4835 4840 4845

Cys Cys Cys Ala Cys Gly Cys Thr Ala Ala Ala Cys Ala Thr Thr
4850 4855 4860

Cys Thr Thr Thr Thr Thr Cys Thr Cys Thr Thr Thr Thr Gly Gly
4865 4870 4875

Thr Thr Ala Ala Ala Thr Cys Gly Thr Thr Gly Thr Thr Thr Gly
4880 4885 4890

Ala Thr Thr Thr Ala Thr Thr Ala Thr Thr Thr Gly Cys Thr Ala
4895 4900 4905

Thr Ala Thr Thr Thr Ala Thr Thr Thr Thr Thr Cys Gly Ala Thr
4910 4915 4920

Ala Ala Thr Thr Ala Thr Cys Ala Ala Cys Thr Ala Gly Ala Gly
4925 4930 4935

Ala Ala Gly Gly Ala Ala Cys Ala Ala Thr Thr Ala Ala Thr Gly
4940 4945 4950

Gly Thr Ala Thr Gly Thr Thr Cys Ala Thr Ala Cys Ala Cys Gly
4955 4960 4965

Cys Ala Thr Gly Thr Ala Ala Ala Ala Ala Thr Ala Ala Ala Cys
4970 4975 4980

Thr Ala Thr Cys Thr Ala Thr Ala Thr Ala Gly Thr Thr Gly Thr
4985 4990 4995

Cys Thr Thr Thr Cys Thr Cys Thr Gly Ala Ala Thr Gly Thr Gly
5000 5005 5010

Cys Ala Ala Ala Ala Cys Thr Ala Ala Gly Cys Ala Thr Thr Cys
5015 5020 5025

Cys Gly Ala Ala Gly Cys Cys Ala Thr Thr Ala Thr Thr Ala Gly
5030 5035 5040

Cys Ala Gly Thr Ala Thr Gly Ala Ala Thr Ala Gly Gly Gly Ala
5045 5050 5055

Ala Ala Cys Thr Ala Ala Ala Cys Cys Cys Ala Gly Thr Gly Ala
5060 5065 5070

Thr Ala Ala Gly Ala Cys Cys Thr Gly Ala Thr Gly Ala Thr Thr
5075 5080 5085

Thr Cys Gly Cys Thr Thr Cys Thr Thr Thr Ala Ala Thr Thr Ala
5090 5095 5100

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5120 5125 5130

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Gly Ala Thr Thr Gly Gly Ala Gly Thr Thr Ala Gly Ala Ala Thr
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Ala Ala Thr Cys Thr Ala Cys Thr Ala Thr Ala Gly Gly Ala Thr
5180 5185 5190

Cys Ala Thr Ala Thr Thr Thr Thr Ala Thr Thr Ala Ala Ala Thr
5195 5200 5205

Thr Ala Gly Cys Gly Thr Cys Ala Thr Cys Ala Thr Ala Ala Thr
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5225 5230 5235

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5240 5245 5250

Gly Ala Ala Thr Thr Gly Ala Ala Ala Thr Ala Thr Cys Ala Gly
5255 5260 5265

Ala Thr Thr Thr Ala Ala Cys Cys Ala Thr Ala Gly Ala Ala Thr
5270 5275 5280

Gly Ala Gly Gly Ala Thr Ala Ala Ala Thr Gly Ala Thr Cys Gly
5285 5290 5295

Cys Gly Ala Gly Thr Ala Ala Ala Thr Ala Ala Thr Ala Thr Thr
5300 5305 5310

Cys Ala Cys Ala Ala Thr Gly Thr Ala Cys Cys Ala Thr Thr Thr
5315 5320 5325

Thr Ala Gly Thr Cys Ala Thr Ala Thr Cys Ala Gly Ala Thr Ala
5330 5335 5340

Ala Gly Cys Ala Thr Thr Gly Ala Thr Thr Ala Ala Thr Ala Thr
5345 5350 5355

Cys Ala Thr Thr Ala Thr Thr Gly Cys Thr Thr Cys Thr Ala Cys
5360 5365 5370

Ala Gly Gly Cys Thr Thr Thr Ala Ala Thr Thr Thr Thr Ala Thr
5375 5380 5385

Thr Ala Ala Thr Thr Ala Thr Thr Cys Thr Gly Thr Ala Ala Gly
5390 5395 5400

Thr Gly Thr Cys Gly Thr Cys Gly Gly Cys Ala Thr Thr Thr Ala
5405 5410 5415

Thr Gly Thr Cys Thr Thr Thr Cys Ala Thr Ala Cys Cys Cys Ala
5420 5425 5430

Thr Cys Thr Cys Thr Thr Thr Ala Thr Cys Cys Thr Thr Ala Cys
5435 5440 5445

Cys Thr Ala Thr Thr Gly Thr Thr Thr Gly Thr Cys Gly Cys Ala
5450 5455 5460

Ala Gly Thr Thr Thr Thr Gly Cys Gly Thr Gly Thr Thr Ala Thr
5465 5470 5475

Ala Thr Ala Thr Cys Ala Thr Thr Ala Ala Ala Ala Cys Gly Gly
5480 5485 5490

Thr Ala Ala Thr Ala Gly Ala Thr Thr Gly Ala Cys Ala Thr Thr
5495 5500 5505

Thr Gly Ala Thr Thr Cys Thr Ala Ala Thr Ala Ala Ala Thr Thr
5510 5515 5520

Gly Gly Ala Thr Thr Thr Thr Thr Gly Thr Cys Ala Cys Ala Cys
5525 5530 5535

Thr Ala Thr Thr Ala Thr Ala Thr Cys Gly Cys Thr Thr Gly Ala
5540 5545 5550

Ala Ala Thr Ala Cys Ala Ala Thr Thr Gly Thr Thr Thr Ala Ala
5555 5560 5565

Cys Ala Thr Ala Ala Gly Thr Ala Cys Cys Thr Gly Thr Ala Gly
5570 5575 5580

Gly Ala Thr Cys Gly Thr Ala Cys Ala Gly Gly Thr Thr Thr Ala
5585 5590 5595

Cys Gly Cys Ala Ala Gly Ala Ala Ala Ala Thr Gly Gly Thr Thr
5600 5605 5610

Thr Gly Thr Thr Ala Thr Ala Gly Thr Cys Gly Ala Thr Thr Ala
5615 5620 5625

Ala Thr Cys Gly Ala Thr Thr Thr Gly Ala Thr Thr Cys Thr Ala
5630 5635 5640

Gly Ala Thr Thr Thr Gly Thr Thr Thr Thr Ala Ala Cys Thr Ala
5645 5650 5655

Ala Thr Thr Ala Ala Ala Gly Gly Ala Gly Gly Ala Ala Thr Ala
5660 5665 5670

Ala Cys Ala Thr Ala Thr Gly Ala Thr Cys Gly Cys Thr Cys Cys
5675 5680 5685

Ala Cys Cys Ala Thr Gly Cys Ala Cys Cys Ala Gly Thr Gly Ala
5690 5695 5700

Gly Ala Ala Gly Cys Ala Thr Thr Ala Thr Gly Ala Gly Cys Ala
5705 5710 5715

Thr Cys Thr Gly Gly Gly Ala Cys Gly Gly Thr Gly Cys Thr Gly
5720 5725 5730

Thr Ala Ala Cys Ala Ala Ala Thr Gly Thr Gly Ala Ala Cys Cys
5735 5740 5745

Ala Gly Gly Ala Ala Ala Gly Thr Ala Cys Ala Thr Gly Thr Cys
5750 5755 5760

Thr Thr Cys Thr Ala Ala Ala Thr Gly Cys Ala Cys Thr Ala Cys
5765 5770 5775

Thr Ala Cys Cys Thr Cys Thr Gly Ala Cys Ala Gly Thr Gly Thr
5780 5785 5790

Ala Thr Gly Thr Cys Thr Gly Cys Cys Cys Thr Gly Thr Gly Gly
5795 5800 5805

Cys Cys Cys Gly Gly Ala Thr Gly Ala Ala Thr Ala Cys Thr Thr
5810 5815 5820

Gly Gly Ala Thr Ala Gly Cys Thr Gly Gly Ala Ala Thr Gly Ala
5825 5830 5835

Ala Gly Ala Ala Gly Ala Thr Ala Ala Ala Thr Gly Cys Thr Thr
5840 5845 5850

Gly Cys Thr Gly Cys Ala Thr Ala Ala Ala Gly Thr Thr Thr Gly
5855 5860 5865

Thr Gly Ala Thr Ala Cys Ala Gly Gly Cys Ala Ala Gly Gly Cys
5870 5875 5880

Cys Cys Thr Gly Gly Thr Gly Gly Cys Cys Gly Thr Gly Gly Thr
5885 5890 5895

Cys Gly Cys Cys Gly Gly Cys Ala Ala Cys Ala Gly Thr Ala Cys
5900 5905 5910

Gly Ala Cys Cys Cys Cys Cys Cys Gly Gly Cys Gly Cys Thr Gly
5915 5920 5925

Cys Gly Cys Gly Thr Gly Cys Ala Cys Gly Gly Cys Thr Gly Gly
5930 5935 5940

Gly Thr Ala Cys Cys Ala Cys Thr Gly Gly Ala Gly Cys Cys Ala
5945 5950 5955

Gly Gly Ala Cys Thr Gly Cys Gly Ala Gly Thr Gly Cys Thr Gly
5960 5965 5970

Cys Cys Gly Cys Cys Gly Cys Ala Ala Cys Ala Cys Cys Gly Ala
5975 5980 5985

Gly Thr Gly Cys Gly Cys Gly Cys Cys Gly Gly Gly Cys Cys Thr
5990 5995 6000

Gly Gly Gly Cys Gly Cys Cys Cys Ala Gly Cys Ala Cys Cys Cys
6005 6010 6015

Gly Thr Thr Gly Cys Ala Gly Cys Thr Cys Ala Ala Cys Ala Ala
6020 6025 6030

Gly Gly Ala Cys Ala Cys Ala Gly Thr Gly Thr Gly Cys Ala Ala
6035 6040 6045

Ala Cys Cys Thr Thr Gly Cys Cys Thr Thr Gly Cys Ala Gly Gly
6050 6055 6060

Cys Thr Ala Cys Thr Thr Cys Thr Cys Thr Gly Ala Thr Gly Cys
6065 6070 6075

Cys Thr Thr Thr Thr Cys Cys Thr Cys Cys Ala Cys Gly Gly Ala
6080 6085 6090

Cys Ala Ala Ala Thr Gly Cys Ala Gly Ala Cys Cys Cys Thr Gly
6095 6100 6105

Gly Ala Cys Cys Ala Ala Cys Thr Gly Thr Ala Cys Cys Thr Thr
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Cys Cys Thr Thr Gly Gly Ala Ala Ala Gly Ala Gly Ala Gly Thr
6125 6130 6135

Ala Gly Ala Ala Cys Ala Thr Cys Ala Thr Gly Gly Gly Ala Cys
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Gly Gly Thr Thr Thr Gly Cys Ala Gly Thr Thr Cys Thr Thr Cys
6170 6175 6180

Thr Cys Thr Gly Cys Cys Ala Gly Cys Thr Ala Gly Ala Ala Ala
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Ala Cys Cys Ala Cys Cys Ala Ala Ala Thr Gly Ala Ala Cys Cys
6200 6205 6210

Cys Cys Ala Thr Gly Thr Thr Thr Ala Cys Gly Thr Cys Gly Ala
6215 6220 6225

Cys Ala Ala Ala Ala Cys Thr Cys Ala Cys Ala Cys Ala Thr Gly
6230 6235 6240

Thr Cys Cys Ala Cys Cys Thr Thr Gly Thr Cys Cys Ala Gly Cys
6245 6250 6255

Thr Cys Cys Gly Gly Ala Ala Cys Thr Cys Cys Thr Gly Gly Gly
6260 6265 6270

Gly Gly Gly Ala Cys Cys Gly Thr Cys Ala Gly Thr Cys Thr Thr
6275 6280 6285

Cys Cys Thr Cys Thr Thr Cys Cys Cys Cys Cys Ala Ala Ala
6290 6295 6300

Ala Cys Cys Cys Ala Ala Gly Gly Ala Cys Ala Cys Cys Cys Thr
6305 6310 6315

Cys Ala Thr Gly Ala Thr Cys Thr Cys Cys Cys Gly Gly Ala Cys
6320 6325 6330

Cys Cys Cys Thr Gly Ala Gly Gly Thr Cys Ala Cys Ala Thr Gly
6335 6340 6345

Cys Gly Thr Gly Gly Thr Gly Gly Thr Gly Gly Ala Cys Gly Thr
6350 6355 6360

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6365 6370 6375

Thr Gly Ala Gly Gly Thr Cys Ala Ala Gly Thr Thr Cys Ala Ala
6380 6385 6390

Cys Thr Gly Gly Thr Ala Cys Gly Thr Gly Gly Ala Cys Gly Gly
6395 6400 6405

Cys Gly Thr Gly Gly Ala Gly Gly Thr Gly Cys Ala Thr Ala Ala
6410 6415 6420

Thr Gly Cys Cys Ala Ala Gly Ala Cys Ala Ala Ala Gly Cys Cys
6425 6430 6435

Gly Cys Gly Gly Gly Ala Gly Gly Ala Gly Cys Ala Gly Thr Ala
6440 6445 6450

Cys Ala Ala Cys Ala Gly Cys Ala Cys Gly Thr Ala Cys Cys Gly
6455 6460 6465

Thr Gly Thr Gly Gly Thr Cys Ala Gly Cys Gly Thr Cys Cys Thr
6470 6475 6480

Cys Ala Cys Cys Gly Thr Cys Cys Thr Gly Cys Ala Cys Cys Ala
6485 6490 6495

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6500 6505 6510

Cys Ala Ala Gly Gly Ala Gly Thr Ala Cys Ala Ala Gly Thr Gly
6515 6520 6525

Cys Ala Ala Gly Gly Thr Cys Thr Cys Cys Ala Ala Cys Ala Ala
6530 6535 6540

Ala Gly Cys Cys Cys Thr Cys Cys Cys Ala Gly Cys Cys Cys Cys
6545 6550 6555

Cys Ala Thr Cys Gly Ala Gly Ala Ala Ala Ala Cys Cys Ala Thr
6560 6565 6570

Cys Thr Cys Cys Ala Ala Ala Gly Cys Cys Ala Ala Ala Gly Gly
6575 6580 6585

Gly Cys Ala Gly Cys Cys Cys Cys Gly Ala Gly Ala Ala Cys Cys
6590 6595 6600

Ala Cys Ala Gly Gly Thr Gly Thr Ala Cys Ala Cys Cys Cys Thr
6605 6610 6615

Gly Cys Cys Cys Cys Cys Ala Thr Cys Cys Cys Gly Gly Gly Ala
6620 6625 6630

Thr Gly Ala Gly Cys Thr Gly Ala Cys Cys Ala Ala Gly Ala Ala
6635 6640 6645

Cys Cys Ala Gly Gly Thr Cys Ala Gly Cys Cys Thr Gly Ala Cys
6650 6655 6660

Cys Thr Gly Cys Cys Thr Gly Gly Thr Cys Ala Ala Ala Gly Gly
6665 6670 6675

Cys Thr Thr Cys Thr Ala Thr Cys Cys Cys Ala Gly Cys Gly Ala
6680 6685 6690

Cys Ala Thr Cys Gly Cys Cys Gly Thr Gly Gly Ala Gly Thr Gly
6695 6700 6705

Gly Gly Ala Gly Ala Gly Cys Ala Ala Thr Gly Gly Gly Cys Ala
6710 6715 6720

Gly Cys Cys Gly Gly Ala Gly Ala Ala Cys Ala Ala Cys Thr Ala
6725 6730 6735

Cys Ala Ala Gly Ala Cys Cys Ala Cys Gly Cys Cys Thr Cys Cys
6740 6745 6750

Cys Gly Thr Gly Cys Thr Gly Gly Ala Cys Thr Cys Cys Gly Ala
6755 6760 6765

Cys Gly Gly Cys Thr Cys Cys Thr Thr Cys Thr Thr Cys Cys Thr
6770 6775 6780

Cys Thr Ala Cys Ala Gly Cys Ala Ala Gly Cys Thr Cys Ala Cys
6785 6790 6795

Cys Gly Thr Gly Gly Ala Cys Ala Ala Gly Ala Gly Cys Ala Gly
6800 6805 6810

Gly Thr Gly Gly Cys Ala Gly Cys Ala Gly Gly Gly Gly Ala Ala
6815 6820 6825

Cys Gly Thr Cys Thr Thr Cys Thr Cys Ala Thr Gly Cys Thr Cys
6830 6835 6840

Cys Gly Thr Gly Ala Thr Gly Cys Ala Thr Gly Ala Gly Gly Cys
6845 6850 6855

Thr Cys Thr Gly Cys Ala Cys Ala Ala Cys Cys Ala Cys Thr Ala
6860 6865 6870

Cys Ala Cys Gly Cys Ala Gly Ala Ala Gly Ala Gly Cys Cys Thr
6875 6880 6885

Cys Thr Cys Cys Cys Thr Gly Thr Cys Thr Cys Cys Gly Gly Gly
6890 6895 6900

Thr Ala Ala Ala Thr Ala Ala Thr Gly Gly Ala Thr Cys Cys Gly
6905 6910 6915

Cys Gly Gly Ala Ala Ala Gly Ala Ala Gly Ala Ala Gly Ala Ala
6920 6925 6930

Gly Ala Ala Gly Ala Ala Gly Ala Ala Ala Gly Cys Cys Cys Gly
6935 6940 6945

Ala Ala Ala Gly Gly Ala Ala Gly Cys Thr Gly Ala Gly Thr Thr
6950 6955 6960

Gly Gly Cys Thr Gly Cys Thr Gly Cys Cys Ala Cys Cys Gly Cys
6965 6970 6975

Thr Gly Ala Gly Cys Ala Ala Thr Ala Ala Cys Thr Ala Gly Cys
6980 6985 6990

Ala Thr Ala Ala Cys Cys Cys Cys Thr Thr Gly Gly Gly Gly Cys
6995 7000 7005

Cys Thr Cys Thr Ala Ala Ala Cys Gly Gly Gly Thr Cys Thr Thr
7010 7015 7020

Gly Ala Gly Gly Gly Gly Thr Thr Thr Thr Thr Gly Cys Thr
7025 7030 7035

Gly Ala Ala Ala Gly Gly Ala Gly Gly Ala Ala Cys Cys Gly Cys
7040 7045 7050

Thr Cys Thr Thr Cys Ala Cys Gly Cys Thr Cys Thr Thr Cys Ala
7055 7060 7065

Cys Gly Cys Gly Gly Ala Thr Ala Ala Ala Thr Ala Ala Gly Thr
7070 7075 7080

Ala Ala Cys Gly Ala Thr Cys Cys Gly Gly Thr Cys Cys Ala Gly
7085 7090 7095

Thr Ala Ala Thr Gly Ala Cys Cys Thr Cys Ala Gly Ala Ala Cys
7100 7105 7110

Thr Cys Cys Ala Thr Cys Thr Gly Gly Ala Thr Thr Thr Gly Thr
7115 7120 7125

Thr Cys Ala Gly Ala Ala Cys Gly Cys Thr Cys Gly Gly Thr Thr
7130 7135 7140

Gly Cys Cys Gly Cys Cys Gly Gly Gly Cys Gly Thr Thr Thr Thr
7145 7150 7155

Thr Thr Ala Thr Thr Gly Gly Thr Gly Ala Gly Ala Ala Thr Cys
7160 7165 7170

Gly Cys Ala Gly Cys Ala Ala Cys Thr Thr Gly Thr Cys Gly Cys
7175 7180 7185

Gly Cys Cys Ala Ala Thr Cys Gly Ala Gly Cys Cys Ala Thr Gly
7190 7195 7200

Thr Cys Gly Thr Cys Gly Thr Cys Ala Ala Cys Gly Ala Cys Cys
7205 7210 7215

Cys Cys Cys Cys Ala Thr Thr Cys Ala Ala Gly Ala Ala Cys Ala
7220 7225 7230

Gly Cys Ala Ala Gly Cys Ala Gly Cys Ala Thr Thr Gly Ala Gly
7235 7240 7245

Ala Ala Cys Thr Thr Thr Gly Gly Ala Ala Thr Cys Cys Ala Gly
7250 7255 7260

Thr Cys Cys Cys Thr Cys Thr Thr Cys Cys Ala Cys Cys Thr Gly
7265 7270 7275

Cys Thr Gly Ala Cys Cys Gly
7280 7285

<210> 29
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 Modulating Domains

<400> 29

Pro Gly Thr Cys Phe Pro Phe Pro Trp Glu Cys Thr His Ala
1 5 10

<210> 30
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 Modulating Domains

<400> 30

Trp Gly Ala Cys Trp Pro Phe Pro Trp Glu Cys Phe Lys Glu
1 5 10

<210> 31
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 Modulating Domains

<400> 31

Val Pro Phe Cys Asp Leu Leu Thr Lys His Cys Phe Glu Ala
1 5 10

<210> 32
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 Modulating Domains

<400> 32

Gly Ser Arg Cys Lys Tyr Lys Trp Asp Val Leu Thr Lys Gln Cys Phe
1 5 10 15

His His

<210> 33
<211> 18
<212> PRT

<213> Artificial Sequence

<220>
<223> Preferred TALL-1 Modulating Domains

<400> 33

Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys Asp
1 5 10 15

Pro Leu

<210> 34
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 Modulating Domains

<400> 34

Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Cys Thr
1 5 10 15

Ser Ser

<210> 35
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 Modulating Domains

<400> 35

Ser Asp Asp Cys Met Tyr Asp Gln Leu Thr Arg Met Phe Ile Cys Ser
1 5 10 15

Asn Leu

<210> 36
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 Modulating Domains

<400> 36

Asp Leu Asn Cys Lys Tyr Asp Glu Leu Thr Tyr Lys Glu Trp Cys Gln
1 5 10 15

Phe Asn

<210> 37
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 Modulating Domains

<400> 37

Phe His Asp Cys Lys Tyr Asp Leu Leu Thr Arg Gln Met Val Cys His
1 5 10 15

Gly Leu

<210> 38
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 Modulating Domains

<400> 38

Arg Asn His Cys Phe Trp Asp His Leu Leu Lys Gln Asp Ile Cys Pro
1 5 10 15

Ser Pro

<210> 39
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 Modulating Domains

<400> 39

Ala Asn Gln Cys Trp Trp Asp Ser Leu Thr Lys Lys Asn Val Cys Glu
1 5 10 15

Phe Phe

<210> 40
<211> 8
<212> DNA
<213> Artificial Sequence

<220>
<223> Polyglycine linkers

<400> 40
gggkgggg 8

<210> 41

<211> 8
<212> DNA
<213> Artificial Sequence

<220>
<223> Polyglycine linkers

<220>
<221> misc_feature
<222> (4)..(4)
<223> N is aspargine

<400> 41
gggngsgg 8

<210> 42
<211> 8
<212> DNA
<213> Artificial Sequence

<220>
<223> Polyglycine linkers

<400> 42
gggcgggg 8

<210> 43
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Polyglycine linkers

<400> 43

Gly Pro Asn Gly Gly
1 5

<210> 44
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide Bond

<220>
<221> misc_feature
<222> (19)..(19)
<223> Xaa = a peptide bond
Fc domain attached at Position 19 to C-terminus

<400> 44

Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys Asp
1 5 10 15

Pro Leu Xaa

<210> 45
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide bond

<220>
<221> misc_feature
<222> (1)..(1)
<223> Xaa = a peptide bond
Fc domain attached at Position 1 to N-terminus

<400> 45

Xaa Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys
1 5 10 15

Asp Pro Leu

<210> 46
<211> 38
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide bond

<220>
<221> misc_feature
<222> (38)..(38)
<223> Xaa = a peptide bond
Fc domain attached at Position 38 to C-terminus

<220>
<221> misc_feature
<222> (19)..(19)
<223> Xaa = a peptide bond

<400> 46

Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys Asp
1 5 10 15

Pro Leu Xaa Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp
20 25 30

Val Cys Asp Pro Leu Xaa
35

<210> 47
<211> 38
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide bond

<220>
<221> misc_feature
<222> (1)..(1)
<223> Xaa = a peptide bond
Fc domain attached at Position 1 to N-terminus

<220>
<221> misc_feature
<222> (20)..(20)
<223> Xaa = a peptide bond

<400> 47

Xaa Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys
1 5 10 15

Asp Pro Leu Xaa Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln
20 25 30

Trp Val Cys Asp Pro Leu
35

<210> 48
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide bond

<220>
<221> misc_feature
<222> (19)..(19)
<223> Xaa = a peptide bond
Fc domain attached at Position 19 to C-terminus

<400> 48

Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Cys Thr
1 5 10 15

Ser Ser Xaa

<210> 49
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide bond

<220>
<221> misc_feature
<222> (1)..(1)
<223> Xaa = a peptide bond
Fc domain attached at Position 1 to N-terminus

<400> 49

Xaa Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Cys
1 5 10 15

Thr Ser Ser

<210> 50
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide bond

<220>
<221> misc_feature
<222> (36)..(36)
<223> Xaa = a peptide bond
Fc domain attached at Position 36 to C-terminus

<220>
<221> misc_feature
<222> (18)..(18)
<223> Xaa = a peptide bond

<400> 50

Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Thr Ser
1 5 10 15

Ser Xaa Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val
20 25 30

Thr Ser Ser Xaa
35

<210> 51
<211> 36
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide bond

<220>
<221> misc_feature
<222> (1)..(1)
<223> Xaa = a peptide bond
Fc domain attached at Position 1 to N-terminus

<220>
<221> misc_feature
<222> (19)..(19)
<223> Xaa = a peptide bond

<400> 51

Xaa Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Thr

1 5 10 15

Ser Ser Xaa Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp
20 25 30

Val Thr Ser Ser
35

<210> 52
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide bond

<220>
<221> misc_feature
<222> (19)..(19)
<223> Xaa = a peptide bond
Fc domain attached at Position 19 to C-terminus

<400> 52

Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys His
1 5 10 15

Gly Leu Xaa

<210> 53
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide bond

<220>
<221> misc_feature
<222> (1)..(1)
<223> Xaa = a peptide bond
Fc domain attached at Position 1 to N-terminus

<400> 53

Xaa Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys
1 5 10 15

His Gly Leu

<210> 54
<211> 38
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide bond

<220>
<221> misc_feature
<222> (19)..(19)
<223> Xaa = a peptide bond

<220>
<221> misc_feature
<222> (38)..(38)
<223> Xaa = a peptide bond
Fc domain attached at Position 38 to C-terminus

<400> 54

Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys His
1 5 10 15

Gly Leu Xaa Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp
20 25 30

Val Cys His Gly Leu Xaa
35

<210> 55
<211> 38
<212> PRT
<213> Artificial Sequence

<220>
<223> Peptide bond

<220>
<221> misc_feature
<222> (1)..(1)
<223> Xaa = a peptide bond
Fc domain attached at Position 1 to N-terminus

<220>
<221> misc_feature
<222> (20)..(20)
<223> Xaa = a peptide bond

<400> 55

Xaa Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys
1 5 10 15

His Gly Leu Xaa Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln
20 25 30

Trp Val Cys His Gly Leu
35

<210> 56
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 56
cggcgcaact atcggtatca agctg 25

<210> 57
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotide

<400> 57
catgtaccgt aacactgagt ttcgtc 26

<210> 58
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Consensus peptide

<400> 58

Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys His
1 5 10 15

Gly Leu

<210> 59
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred linker sequence

<400> 59

Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly
1 5 10 15

Ser Gly Ser Ala Thr His Met
20

<210> 60
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 60

Asn Gln Thr Leu Trp Lys Trp Asp Leu Leu Thr Lys Gln Phe Ile Thr
1 5 10 15

Tyr Met

<210> 61
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 61

Pro Val Tyr Gln Gly Trp Trp Asp Thr Leu Thr Lys Leu Tyr Ile Trp
1 5 10 15

Asp Gly

<210> 62
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 62

Trp Leu Asp Gly Gly Trp Arg Asp Pro Leu Ile Lys Arg Ser Val Gln
1 5 10 15

Leu Gly

<210> 63
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 63

Gly His Gln Gln Phe Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Gln
1 5 10 15

Ser Asn

<210> 64
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 64

Gln Arg Val Gly Gln Phe Trp Asp Val Leu Thr Lys Met Phe Ile Thr
1 5 10 15

Gly Ser

<210> 65
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 65

Gln Ala Gln Gly Trp Ser Tyr Asp Ala Leu Ile Lys Thr Trp Ile Arg
1 5 10 15

Trp Pro

<210> 66
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 66

Gly Trp Met His Trp Lys Trp Asp Pro Leu Thr Lys Gln Ala Leu Pro
1 5 10 15

Trp Met

<210> 67
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 67

Gly His Pro Thr Tyr Lys Trp Asp Leu Leu Thr Lys Gln Trp Ile Leu
1 5 10 15

Gln Met

<210> 68
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 68

Trp Asn Asn Trp Ser Leu Trp Asp Pro Leu Thr Lys Leu Trp Leu Gln
1 5 10 15

Gln Asn

<210> 69
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 69

Trp Gln Trp Gly Trp Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Gln
1 5 10 15

Gln Gln

<210> 70
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 70

Gly Gln Met Gly Trp Arg Trp Asp Pro Leu Thr Lys Met Trp Leu Gly
1 5 10 15

Thr Ser

<210> 71
<211> 62
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 71
tatgccgggt acttgtttcc cgttcccgtg ggaatgcact cacgctggtg gaggcggtgg 60

gg 62

<210> 72
<211> 64
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 72
tcgaccccac cgcctcctgg agcgtgagtg cattcccacg ggaagccgaa acaagtaccc 60

ggca 64

<210> 73
<211> 62
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 73
tatgtggggt gcttgttggc cgttcccgtg ggaatgtttc aaagaaggtg gaggcggtgg 60

gg 62

<210> 74
<211> 64
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 74
tcgaccccac cgcctccacc ttctttgaaa cattcccacg ggaacggcca acaagcaccc 60

caca 64

<210> 75
<211> 62
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 75
tatggttccg ttctgtgacc tgctgactaa acactgtttc gaagctggtg gaggcggtgg 60

gg 62

<210> 76
<211> 64
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 76
tcgaccccac cgcctccacc agcttcgaaa cagtgtttag tcagcaggtc acagaacgga 60

acca 64

<210> 77
<211> 74
<212> DNA

<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 77
tatgggttct cgttgtaaat acaaatggga cgttctgact aaacagtgtt tccaccacgg 60

tggaggcggt gggg 74

<210> 78
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 78
tcgaccccac cgcctccacc gtggtggaaa cactgtttag tcagaacgtc ccatttgtat 60

ttacaacgag aaccca 76

<210> 79
<211> 74
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 79
tatgctgccg ggttgtaaat gggacctgct gatcaaacag tgggtttgtg acccgctggg 60

tggaggcggt gggg 74

<210> 80
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 80
tcgaccccac cgcctccacc cagcgggtca caaacccact gtttgatcag caggtcccat 60

ttacaacccg gcagca 76

<210> 81
<211> 74
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 81
tatgtctgct gactgttact tcgacatcct gactaaatct gacgtttgta cttcttctgg 60

tggaggcggt gggg 74

<210> 82

<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 82
tcgaccccac cgcctccacc agaagaagta caaacgtcag atttagtcag gatgtcgaag 60

taacagtcag cagaca 76

<210> 83
<211> 74
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 83
tatgtctgac gactgtatgt acgaccagct gactcgtatg ttcatctgtt ctaacctggg 60

tggaggcggt gggg 74

<210> 84
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 84
tcgaccccac cgcctccacc caggttagaa cagatgaaca tacgagtcag ctggtcgtac 60

atacagtcgt cagaca 76

<210> 85
<211> 74
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 85
tatggacctg aactgtaaat acgacgaact gacttacaaa gaatggtgtc agttcaacgg 60

tggaggcggt gggg 74

<210> 86
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 86
tcgaccccac cgcctccacc gttgaactga caccattctt tgtaagtcag ttcgtcgtat 60

ttacagttca ggtcca 76

<210> 87
<211> 74
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 87
tatgttccac gactgtaaat acgacctgct gactcgtcag atggtttgtc acggtctggg 60

tggaggcggt gggg 74

<210> 88
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 88
tcgaccccac cgcctccacc cagaccgtga caaaccatct gacgagtcag caggtcgtat 60

ttacagtcgt ggaaca 76

<210> 89
<211> 74
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 89
tatgcgtaac cactgtttct gggaccacct gctgaaacag gacatctgtc cgtctccggg 60

tggaggcggt gggg 74

<210> 90
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 90
tcgaccccac cgcctccacc cggagacgga cagatgtcct gtttcagcag gtggtcccag 60

aaacagtggt tacgca 76

<210> 91
<211> 74
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 91
tatggctaac cagtgttggt gggactctct gctgaaaaaa aacgtttgtg aattcttcgg 60

tggaggcggt gggg 74

<210> 92
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 92
tcgaccccac cgcctccacc gaagaattca caaacgtttt ttttcagcag agagtcccac 60

caacactggt tagcca 76

<210> 93
<211> 74
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 93
tatgttccac gactgcaaat gggacctgct gaccaaacag tgggtttgcc acggtctggg 60

tggaggcggt gggg 74

<210> 94
<211> 76
<212> DNA
<213> Artificial Sequence

<220>
<223> Oligonucleotides

<400> 94
tcgaccccac cgcctccacc cagaccgtgg caaacccact gtttggtcag caggtcccat 60

ttgcagtcgt ggaaca 76

<210> 95
<211> 141
<212> DNA
<213> Artificial Sequence

<220>
<223> pAMG21-RANK-Fc vector

<400> 95
ctaattccgc tctcacctac caaacaatgc ccccctgcaa aaaataaatt catataaaaa 60

acatacagat aaccatctgc ggtgataaat tatctctggc ggtgttgaca taaataccac 120

tggcggtgat actgagcaca t 141

<210> 96
<211> 55
<212> DNA
<213> Artificial Sequence

<220>
<223> pAMG21-RANK-Fc vector

<400> 96
cgatttgatt ctagaaggag gaataacata tggttaacgc gttggaattc ggtac 55

<210> 97
<211> 1546
<212> DNA
<213> Artificial Sequence

<220>
<223> pAMG21

<400> 97
gcgtaacgta tgcatggtct ccccatgcga gagtagggaa ctgccaggca tcaaataaaa 60

cgaaaggctc agtcgaaaga ctgggccttt cgttttatct gttgtttgtc ggtgaacgct 120

ctcctgagta ggacaaatcc gccgggagcg gatttgaacg ttgcgaagca acggcccgga 180

gggtggcggg caggacgccc gccataaact gccaggcatc aaattaagca gaaggccatc 240

ctgacggatg gccttttttgc gtttctacaa actcttttgt ttatttttct aaatacattc 300

aaatatggac gtcgtactta acttttaaag tatgggcaat caattgctcc tgttaaaatt 360

gctttagaaa tactttggca gcggtttgtt gtattgagtt tcatttgcgc attggttaaa 420

tggaaagtga ccgtgcgctt actacagcct aatatttttg aaatatccca agagcttttt 480

ccttcgcatg cccacgctaa acattctttt tctcttttgg ttaaatcgtt gtttgattta 540

ttatttgcta tatttatttt tcgataatta tcaactagag aaggaacaat taatggtatg 600

ttcatacacg catgtaaaaa taaactatct atatagttgt ctttctctga atgtgcaaaa 660

ctaagcattc cgaagccatt attagcagta tgaataggga aactaaaccc agtgataaga 720

cctgatgatt tcgcttcttt aattacattt ggagattttt tatttacagc attgttttca 780

aatatattcc aattaatcgg tgaatgattg gagttagaat aatctactat aggatcatat 840

tttattaaat tagcgtcatc ataatattgc ctccattttt tagggtaatt atccagaatt 900

gaaatatcag atttaaccat agaatgagga taaatgatcg cgagtaaata atattcacaa 960

tgtaccattt tagtcatatc agataagcat tgattaatat cattattgct tctacaggct 1020

ttaattttat taattattct gtaagtgtcg tcggcattta tgtctttcat acccatctct 1080

ttatccttac ctattgtttg tcgcaagttt tgcgtgttat atatcattaa aacggtaata 1140

gattgacatt tgattctaat aaattggatt tttgtcacac tattatatcg cttgaaatac 1200

aattgtttaa cataagtacc tgtaggatcg tacaggttta cgcaagaaaa tggtttgtta 1260

tagtcgatta atcgatttga ttctagattt gttttaacta attaaaggag gaataacata 1320

tggttaacgc gttggaattc gagctcacta gtgtcgacct gcagggtacc atggaagctt 1380

actcgaggat ccgcggaaag aagaagaaga agaagaaagc ccgaaaggaa gctgagttgg 1440

ctgctgccac cgctgagcaa taactagcat aacccccttgg ggcctctaaa cgggtcttga 1500

ggggtttttt gctgaaagga ggaaccgctc ttcacgctct tcacgc 1546

<210> 98

<211> 872
<212> DNA
<213> Artificial Sequence

<220>
<223> GM221

<400> 98
ttattttcgt gcggccgcac cattatcacc gccagaggta aactagtcaa cacgcacggt 60

gttagatatt tatcccttgc ggtgatagat tgagcacatc gatttgattc tagaaggagg 120

gataatatat gagcacaaaa aagaaaccat taacacaaga gcagcttgag gacgcacgtc 180

gccttaaagc aatttatgaa aaaaagaaaa atgaacttgg cttatcccag gaatctgtcg 240

cagacaagat ggggatgggg cagtcaggcg ttggtgcttt atttaatggc atcaatgcat 300

taaatgctta taacgccgca ttgcttacaa aaattctcaa agttagcgtt gaagaattta 360

gcccttcaat cgccagagaa tctacgagat gtatgaagcg gttagtatgc agccgtcact 420

tagaagtgag tatgagtacc ctgtttttc tcatgttcag gcagggatgt tctcacctaa 480

gcttagaacc tttaccaaag gtgatgcgga gagatgggta agcacaacca aaaaagccag 540

tgattctgca ttctggcttg aggttgaagg taattccatg accgcaccaa caggctccaa 600

gccaagcttt cctgacggaa tgttaattct cgttgaccct gagcaggctg ttgagccagg 660

tgatttctgc atagccagac ttgggggtga tgagtttacc ttcaagaaac tgatcaggga 720

tagcggtcag gtgtttttac aaccactaaa cccacagtac ccaatgatcc catgcaatga 780

gagttgttcc gttgtgggga aagttatcgc tagtcagtgg cctgaagaga cgtttggctg 840

atagactagt ggatccacta gtgtttctgc cc 872

<210> 99
<211> 1197
<212> DNA
<213> Artificial Sequence

<220>
<223> GM221

<400> 99
ggcggaaacc gacgtccatc gaatggtgca aaacctttcg cggtatggca tgatagcgcc 60

cggaagagag tcaattcagg gtggtgaatg tgaaaccagt aacgttatac gatgtcgcag 120

agtatgccgg tgtctcttat cagaccgttt cccgcgtggt gaaccaggcc agccacgttt 180

ctgcgaaaac gcgggaaaaa gtcgaagcgg cgatggcgga gctgaattac attcccaacc 240

gcgtggcaca acaactggcg ggcaaacagt cgctcctgat tggcgttgcc acctccagtc 300

tggccctgca cgcgccgtcg caaattgtcg cggcgattaa atctcgcgcc gatcaactgg 360

gtgccagcgt ggtggtgtcg atggtagaac gaagcggcgt cgaagcctgt aaagcggcgg 420

tgcacaatct tctcgcgcaa cgcgtcagtg ggctgatcat taactatccg ctggatgacc 480

aggatgccat tgctgtggaa gctgcctgca ctaatgttcc ggcgttattt cttgatgtct 540

ctgaccagac acccatcaac agtattattt tctcccatga agacggtacg cgactgggcg 600

tggagcatct ggtcgcattg ggtcaccagc aaatcgcgct gttagcgggc ccattaagtt 660

ctgtctcggc gcgtctgcgt ctggctggct ggcataaata tctcactcgc aatcaaattc 720

agccgatagc ggaacgggaa ggcgactgga gtgccatgtc cggttttcaa caaaccatgc 780

aaatgctgaa tgagggcatc gttcccactg cgatgctggt tgccaacgat cagatggcgc 840

tgggcgcaat gcgcgccatt accgagtccg ggctgcgcgt tggtgcggat atctcggtag 900

tgggatacga cgataccgaa gacagctcat gttatatccc gccgttaacc accatcaaac 960

aggattttcg cctgctgggg caaaccagcg tggaccgctt gctgcaactc tctcagggcc 1020

aggcggtgaa gggcaatcag ctgttgcccg tctcactggt gaaaagaaaa accaccctgg 1080

cgcccaatac gcaaaccgcc tctccccgcg cgttggccga ttcattaatg cagctggcac 1140

gacaggtttc ccgactggaa agcggacagt aaggtaccat aggatccagg cacagga 1197

<210> 100
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Modulators of TALL-1

<220>
<221> misc_feature
<222> (1, 2, 3, 13)..(14)
<223> Xaa (Pos1,2,3,13,14) are each independently absent or amino acid residues;

<220>
<221> misc_feature
<222> (6)..(6)
<223> Xaa (Pos6) is an amino acid residue; Xaa (Pos9) is a basic or hyd rophobic residue;

<220>
<221> misc_feature
<222> (12)..(12)
<223> Xaa (Pos12) is a neutral hydrophobic residue.

<400> 100

Xaa Xaa Xaa Cys Asp Xaa Leu Thr Xaa Xaa Cys Xaa Xaa Xaa
1 5 10

<210> 101
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Modulators of TALL-1

<220>
<221> misc_feature
<222> (1, 2, 3, 12 and)..(13)
<223> Xaa (Pos1,2,3,12,13) are each independently absent or amino acid

residues;

<220>
<221> misc_feature
<222> (5 and)..(8)
<223> Xaa (Pos5,8) is a neutral hydrophobic residue; Xaa (Pos10) is an acidic residue;

<220>
<221> misc_feature
<222> (14)..(14)
<223> Xaa (Pos14) is absent or is an amino acid residue.

<400> 101

Xaa Xaa Xaa Cys Xaa Pro Phe Xaa Trp Xaa Cys Xaa Xaa Xaa
1 5 10

<210> 102
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Modulator of TALL-1

<220>
<221> misc_feature
<222> (1, 2, 3, 12, 13 and)..(14)
<223> Xaa (Pos1,2,3,12,13,14) are each independently absent or amino acid residues;

<220>
<221> misc_feature
<222> (6 and)..(7)
<223> Xaa (Pos6,7) is a hydrophobic residue;

<220>
<221> misc_feature
<222> (10)..(10)
<223> Xaa (Pos10) is an acidic or polar hydrophobic residue.

<400> 102

Xaa Xaa Xaa Xaa Trp Xaa Xaa Trp Gly Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 103
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Modulator of TALL-1

<220>
<221> misc_feature
<222> (1)..(1)
<223> Xaa (Pos1) is absent or is an amino acid residue;

<220>
<221> misc_feature
<222> (2 and)..(14)
<223> Xaa (Pos2,14) is a neutral hydrophobic residue;

<220>
<221> misc_feature
<222> (3 and)..(10)
<223> Xaa (Pos3,10) is an amino acid residue;

<220>
<221> misc_feature
<222> (5, 6, 7, 8, 12 and)..(13)
<223> Xaa (Pos5,6,7,8,12,13) are each independently amino acid residues
;

<220>
<221> misc_feature
<222> (9)..(9)
<223> Xaa (Pos9) is an acidic residue.

<400> 103

Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa
1 5 10

<210> 104
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Modulator of TALL-1

<220>
<221> misc_feature
<222> (1, 2, 12, 13, 16, 17 and)..(18)
<223> Xaa (Pos1,2,12,13,16,17,18) are each independently absent or amin
o acid residues;

<220>
<221> misc_feature
<222> (3)..(3)
<223> Xaa (Pos3) is an acidic or amide residue;

<220>
<221> misc_feature
<222> (5 and)..(8)
<223> Xaa (Pos5,8) is an amino acid residue;

<220>
<221> misc_feature
<222> (6)..(6)
<223> Xaa (Pos6) is an aromatic residue;

<220>
<221> misc_feature
<222> (11)..(11)

<223> Xaa (Pos11) is a basic residue;

<220>
<221> misc_feature
<222> (14)..(14)
<223> Xaa (Pos14) is a neutral hydrophobic residue.

<400> 104

Xaa Xaa Xaa Cys Xaa Xaa Asp Xaa Leu Thr Xaa Xaa Xaa Xaa Cys Xaa
1 5 10 15

Xaa Xaa

<210> 105
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Modulator of TALL-1

<220>
<221> misc_feature
<222> (1, 2 and)..(3)
<223> Xaa (Pos1,2,3) are each independently absent or amino acid residu
es;

<220>
<221> misc_feature
<222> (5, 7, 14 and)..(16)
<223> Xaa (Pos5,7,14,16) is an amino acid residue;

<220>
<221> misc_feature
<222> (10)..(10)
<223> Xaa (Pos10) is a basic residue;

<220>
<221> misc_feature
<222> (11 and)..(12)
<223> Xaa (Pos11,12) are each independently amino acid residues;

<220>
<221> misc_feature
<222> (13 and)..(17)
<223> Xaa (Pos13,17) is a neutral hydrophobic residue;

<220>
<221> misc_feature
<222> (18)..(18)
<223> Xaa (Pos18) is an amino acid residue or is absent.

<400> 105

Xaa Xaa Xaa Cys Xaa Asp Xaa Leu Thr Xaa Xaa Xaa Xaa Xaa Cys Xaa

1 5 10 15

Xaa Xaa

<210> 106
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Modulator of TALL-1

<220>
<221> misc_feature
<222> (1, 2, 3, 16, 17 and)..(18)
<223> Xaa (Pos1,2,3,16,17,18) are each independently absent or amino ac
id residues;

<220>
<221> misc_feature
<222> (5, 6, 7, 10, 13 and)..(14)
<223> Xaa (Pos5,6,7,10,13,14) are each independently amino acid residue
s.

<400> 106

Xaa Xaa Xaa Cys Xaa Xaa Xaa Trp Asp Xaa Leu Thr Xaa Xaa Cys Xaa
1 5 10 15

Xaa Xaa

<210> 107
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Modulator of TALL-1

<220>
<221> misc_feature
<222> (1,2,3,15,16,17)..(18)
<223> Xaa (Pos1,2,3,15,16,17,18) are each independently absent or amino
acid residues;

<220>
<221> misc_feature
<222> (5, 6, 7, 9 and)..(13)
<223> Xaa (Pos 5,6,7,9 13) are each independently amino acid residues;

<220>
<221> misc_feature
<222> (11)..(11)
<223> Xaa (Pos 11) is T or I; and

<400> 107

Xaa Xaa Xaa Cys Xaa Xaa Xaa Asp Xaa Leu Xaa Lys Xaa Cys Xaa Xaa
1 5 10 15

Xaa Xaa

<210> 108
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Modulator of TALL-1

<220>
<221> misc_feature
<222> (2)..(2)
<223> X at (Pos 2) is an amino acid residue

<220>
<221> misc_feature
<222> (4)..(4)
<223> X at (Pos 4) is threonyl or isoleucyl

<400> 108

Asp Xaa Leu Xaa
1

<210> 109
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Modulator of TALL-1

<220>
<221> misc_feature
<222> (1, 2 and)..(3)
<223> X at (Pos 1, 2, 3) are absent or are amino acid residues (with on
e of X1, X2, and X3 preferred to be C when one of X12,
X13, an
d X14 is C);

<220>
<221> misc_feature
<222> (5)..(5)
<223> X at (Pos 5) is W, Y, or F (W preferred);

<220>
<221> misc_feature
<222> (7)..(7)
<223> X at (Pos 7) is an amino acid residue (L preferred);

<220>
<221> misc_feature
<222> (9)..(9)
<223> X at (Pos 9) is T or I (T preferred);

<220>
<221> misc_feature
<222> (10)..(10)
<223> X at (Pos 10) is K, R, or H (K preferred).

<220>
<221> misc_feature
<222> (12)..(12)
<223> X at (Pos 12) is C, a neutral hydrophobic residue, or a basic res
idue (W, C, or R preferred);

<220>
<221> misc_feature
<222> (13)..(13)
<223> X at (Post 13) is C, a neutral hydrophobic residue or is absent
(V preferred);

<220>
<221> misc_feature
<222> (14)..(14)
<223> X at (Pos 14) is any amino acid residue or is absent.

<400> 109

Xaa Xaa Xaa Lys Xaa Asp Xaa Leu Xaa Xaa Gln Xaa Xaa Xaa
1 5 10

<210> 110
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Modulator of TALL-1

<400> 110

Pro Phe Pro Trp Glu
1 5

<210> 111
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> TALL-1 inhibitory peptibodies

<400> 111

Met Pro Gly Thr Cys Phe Pro Phe Pro Trp Glu Cys Thr His Ala Gly
1 5 10 15

Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
20 25 30

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
35 40 45

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
50 55 60

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
65 70 75 80

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
85 90 95

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
100 105 110

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
115 120 125

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
130 135 140

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
145 150 155 160

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
165 170 175

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
180 185 190

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
195 200 205

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
210 215 220

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
225 230 235 240

Ser Leu Ser Leu Ser Pro Gly Lys
245

<210> 112
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> TALL-1 inhibitory peptibodies

<400> 112

Met Trp Gly Ala Cys Trp Pro Phe Pro Trp Glu Cys Phe Lys Glu Gly
1 5 10 15

Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala

20 25 30

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
35 40 45

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
50 55 60

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
65 70 75 80

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
85 90 95

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
100 105 110

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
115 120 125

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
130 135 140

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
145 150 155 160

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
165 170 175

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
180 185 190

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
195 200 205

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
210 215 220

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
225 230 235 240

Ser Leu Ser Leu Ser Pro Gly Lys
245

<210> 113
<211> 248
<212> PRT
<213> Artificial Sequence

<220>
<223> TALL-1 inhibitory peptibodies

<400> 113

Met Val Pro Phe Cys Asp Leu Leu Thr Lys His Cys Phe Glu Ala Gly
1 5 10 15

Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
20 25 30

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
35 40 45

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
50 55 60

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
65 70 75 80

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
85 90 95

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
100 105 110

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
115 120 125

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
130 135 140

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
145 150 155 160

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
165 170 175

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
180 185 190

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
195 200 205

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
210 215 220

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
225 230 235 240

Ser Leu Ser Leu Ser Pro Gly Lys
245

<210> 114
<211> 252
<212> PRT

<213> Artificial Sequence

<220>
<223> TALL-1 inhibitory peptibodies

<400> 114

Met Gly Ser Arg Cys Lys Tyr Lys Trp Asp Val Leu Thr Lys Gln Cys
1 5 10 15

Phe His His Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

245 250

<210> 115
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> TALL-1 inhibitory peptibodies

<400> 115

Met Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys
1 5 10 15

Asp Pro Leu Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
245 250

<210> 116
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> TALL-1 inhibitory peptibodies

<400> 116

Met Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Cys
1 5 10 15

Thr Ser Ser Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser

195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
245 250

<210> 117
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> TALL-1 inhibitory peptibodies

<400> 117

Met Ser Asp Asp Cys Met Tyr Asp Gln Leu Thr Arg Met Phe Ile Cys
1 5 10 15

Ser Asn Leu Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
245 250

<210> 118
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> TALL-1 inhibitory peptibodies

<400> 118

Met Asp Leu Asn Cys Lys Tyr Asp Glu Leu Thr Tyr Lys Glu Trp Cys
1 5 10 15

Gln Phe Asn Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg

145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
245 250

<210> 119
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> TALL-1 inhibitory peptibodies

<400> 119

Met Phe His Asp Cys Lys Tyr Asp Leu Leu Thr Arg Gln Met Val Cys
1 5 10 15

His Gly Leu Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
245 250

<210> 120
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> TALL-1 inhibitory peptibodies

<400> 120

Met Arg Asn His Cys Phe Trp Asp His Leu Leu Lys Gln Asp Ile Cys
1 5 10 15

Pro Ser Pro Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr

100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
245 250

<210> 121
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> TALL-1 inhibitory peptibodies

<400> 121

Met Ala Asn Gln Cys Trp Trp Asp Ser Leu Thr Lys Lys Asn Val Cys
1 5 10 15

Glu Phe Phe Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
245 250

<210> 122
<211> 252
<212> PRT
<213> Artificial Sequence

<220>
<223> TALL-1 inhibitory peptibodies

<400> 122

Met Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys
1 5 10 15

His Gly Leu Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
35 40 45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val

50 55 60

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
145 150 155 160

Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
165 170 175

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
180 185 190

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
195 200 205

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
210 215 220

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
225 230 235 240

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
245 250

<210> 123
<211> 293
<212> PRT
<213> Artificial Sequence

<220>
<223> TALL-1 inhibitory peptibodies

<400> 123

Met Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys
1 5 10 15

Asp Pro Leu Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala
20 25 30

```
Ser Ser Gly Ser Gly Ser Ala Thr His Met Leu Pro Gly Cys Lys Trp
        35                  40                  45

Asp Leu Leu Ile Lys Gln Trp Val Cys Asp Pro Leu Gly Gly Gly Gly
    50                  55                  60

Gly Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
65                  70                  75                  80

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                85                  90                  95

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
            100                 105                 110

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
        115                 120                 125

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
    130                 135                 140

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
145                 150                 155                 160

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
                165                 170                 175

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
            180                 185                 190

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
        195                 200                 205

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    210                 215                 220

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
225                 230                 235                 240

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
                245                 250                 255

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
            260                 265                 270

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
        275                 280                 285

Leu Ser Pro Gly Lys
    290
```

<210> 124
<211> 293
<212> PRT
<213> Artificial Sequence

<220>
<223> TALL-1 inhibitory peptibodies

<400> 124

Met Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys
1 5 10 15

His Gly Leu Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala
20 25 30

Ser Ser Gly Ser Gly Ser Ala Thr His Met Phe His Asp Cys Lys Trp
35 40 45

Asp Leu Leu Thr Lys Gln Trp Val Cys His Gly Leu Gly Gly Gly Gly
50 55 60

Gly Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
65 70 75 80

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
85 90 95

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
100 105 110

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
115 120 125

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
130 135 140

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
145 150 155 160

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
165 170 175

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
180 185 190

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
195 200 205

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
210 215 220

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr

225 230 235 240

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
245 250 255

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
260 265 270

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
275 280 285

Leu Ser Pro Gly Lys
290

<210> 125
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Consensus Sequence

<220>
<221> misc_feature
<222> (1, 2 and)..(3)
<223> X at (Pos 1, 2, 3) are absent or are amino acid residues (with on
e of X1, X2, and X3 preferred to be C when one of X12,
X13, an
d X14 is C);

<220>
<221> misc_feature
<222> (7)..(7)
<223> X at (Pos 7) is an amino acid residue (L preferred);

<220>
<221> misc_feature
<222> (9)..(9)
<223> X at (Pos 9) is T or I (T preferred);

<220>
<221> misc_feature
<222> (12)..(12)
<223> X at (Pos 12) is C, a neutral hydrophobic residue, or a basic res
idue (W, C, or R
preferred);

<220>
<221> misc_feature
<222> (13)..(13)
<223> X at (Pos 13) is C, a neutral hydrophobic residue or is absent (V

preferred);

<220>
<221> misc_feature
<222> (14)..(14)
<223> X at (Pos 14) is any amino acid residue or is absent.

<400> 125

Xaa Xaa Xaa Lys Trp Asp Xaa Leu Xaa Lys Gln Xaa Xaa Xaa
1 5 10

<210> 126
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 126

Tyr Lys Gly Arg Gln Met Trp Asp Ile Leu Thr Arg Ser Trp Val Val
1 5 10 15

Ser Leu

<210> 127
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 127

Gln Asp Val Gly Leu Trp Trp Asp Ile Leu Thr Arg Ala Trp Met Pro
1 5 10 15

Asn Ile

<210> 128
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 128

Gln Asn Ala Gln Arg Val Trp Asp Leu Leu Ile Arg Thr Trp Val Tyr
1 5 10 15

Pro Gln

<210> 129
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 129

Gly Trp Asn Glu Ala Trp Trp Asp Glu Leu Thr Lys Ile Trp Val Leu
1 5 10 15

Glu Gln

<210> 130
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 130

Arg Ile Thr Cys Asp Thr Trp Asp Ser Leu Ile Lys Lys Cys Val Pro
1 5 10 15

Gln Ser

<210> 131
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 131

Gly Ala Ile Met Gln Phe Trp Asp Ser Leu Thr Lys Thr Trp Leu Arg
1 5 10 15

Gln Ser

<210> 132
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 132

Trp Leu His Ser Gly Trp Trp Asp Pro Leu Thr Lys His Trp Leu Gln
1 5 10 15

Lys Val

<210> 133
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 133

Ser Glu Trp Phe Phe Trp Phe Asp Pro Leu Thr Arg Ala Gln Leu Lys
1 5 10 15

Phe Arg

<210> 134
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 134

Gly Val Trp Phe Trp Trp Phe Asp Pro Leu Thr Lys Gln Trp Thr Gln
1 5 10 15

Ala Gly

<210> 135
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 135

Met Gln Cys Lys Gly Tyr Tyr Asp Ile Leu Thr Lys Trp Cys Val Thr
1 5 10 15

Asn Gly

<210> 136
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 136

Leu Trp Ser Lys Glu Val Trp Asp Ile Leu Thr Lys Ser Trp Val Ser
1 5 10 15

Gln Ala

<210> 137
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 137

Lys Ala Ala Gly Trp Trp Phe Asp Trp Leu Thr Lys Val Trp Val Pro
1 5 10 15

Ala Pro

<210> 138
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 138

Ala Tyr Gln Thr Trp Phe Trp Asp Ser Leu Thr Arg Leu Trp Leu Ser
1 5 10 15

Thr Thr

<210> 139
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 139

Ser Gly Gln His Phe Trp Trp Asp Leu Leu Thr Arg Ser Trp Thr Pro
1 5 10 15

Ser Thr

<210> 140
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 140

Leu Gly Val Gly Gln Lys Trp Asp Pro Leu Thr Lys Gln Trp Val Ser
1 5 10 15

Arg Gly

<210> 141
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 141

Val Gly Lys Met Cys Gln Trp Asp Pro Leu Ile Lys Arg Thr Val Cys
1 5 10 15

Val Gly

<210> 142
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 142

Cys Arg Gln Gly Ala Lys Phe Asp Leu Leu Thr Lys Gln Cys Leu Leu
1 5 10 15

Gly Arg

<210> 143
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 143

Gly Gln Ala Ile Arg His Trp Asp Val Leu Thr Lys Gln Trp Val Asp
1 5 10 15

Ser Gln

<210> 144

<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 144

Arg Gly Pro Cys Gly Ser Trp Asp Leu Leu Thr Lys His Cys Leu Asp
1 5 10 15

Ser Gln

<210> 145
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 145

Trp Gln Trp Lys Gln Gln Trp Asp Leu Leu Thr Lys Gln Met Val Trp
1 5 10 15

Val Gly

<210> 146
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 146

Pro Ile Thr Ile Cys Arg Lys Asp Leu Leu Thr Lys Gln Val Val Cys
1 5 10 15

Leu Asp

<210> 147
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 147

Lys Thr Cys Asn Gly Lys Trp Asp Leu Leu Thr Lys Gln Cys Leu Gln
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Gln Ala

<210> 148
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 148

Lys Cys Leu Lys Gly Lys Trp Asp Leu Leu Thr Lys Gln Cys Val Thr
1 5 10 15

Glu Val

<210> 149
<211> 18
<212> PRT
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<220>
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Arg Cys Trp Asn Gly Lys Trp Asp Leu Leu Thr Lys Gln Cys Ile His
1 5 10 15

Pro Trp

<210> 150
<211> 18
<212> PRT
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<220>
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<400> 150

Asn Arg Asp Met Arg Lys Trp Asp Pro Leu Ile Lys Gln Trp Ile Val
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Arg Pro

<210> 151
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 151

Gln Ala Ala Ala Ala Thr Trp Asp Leu Leu Thr Lys Gln Trp Leu Val

1 5 10 15

Pro Pro

<210> 152
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 152

Pro Glu Gly Gly Pro Lys Trp Asp Pro Leu Thr Lys Gln Phe Leu Pro
1 5 10 15

Pro Val

<210> 153
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 153

Gln Thr Pro Gln Lys Lys Trp Asp Leu Leu Thr Lys Gln Trp Phe Thr
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Arg Asn

<210> 154
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

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Ile Gly Ser Pro Cys Lys Trp Asp Leu Leu Thr Lys Gln Met Ile Cys
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Gln Thr

<210> 155
<211> 18
<212> PRT
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<220>
<223> Preferred TALL-1 modulating domains

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Cys Thr Ala Ala Gly Lys Trp Asp Leu Leu Thr Lys Gln Cys Ile Gln
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Glu Lys

<210> 156
<211> 18
<212> PRT
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<220>
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<400> 156

Val Ser Gln Cys Met Lys Trp Asp Leu Leu Thr Lys Gln Cys Leu Gln
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Gly Trp

<210> 157
<211> 18
<212> PRT
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<220>
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<400> 157

Val Trp Gly Thr Trp Lys Trp Asp Leu Leu Thr Lys Gln Tyr Leu Pro
1 5 10 15

Pro Gln

<210> 158
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 158

Gly Trp Trp Glu Met Lys Trp Asp Leu Leu Thr Lys Gln Trp Tyr Arg
1 5 10 15

Pro Gln

<210> 159
<211> 18
<212> PRT

<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 159

Thr Ala Gln Val Ser Lys Trp Asp Leu Leu Thr Lys Gln Trp Leu Pro
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Leu Ala

<210> 160
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 160

Gln Leu Trp Gly Thr Lys Trp Asp Leu Leu Thr Lys Gln Tyr Ile Gln
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Ile Met

<210> 161
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 161

Trp Ala Thr Ser Gln Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Gln
1 5 10 15

Asn Met

<210> 162
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 162

Gln Arg Gln Cys Ala Lys Trp Asp Leu Leu Thr Lys Gln Cys Val Leu
1 5 10 15

Phe Tyr

<210> 163
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 163

Lys Thr Thr Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Arg Ile Cys
1 5 10 15

Gln Val

<210> 164
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 164

Leu Leu Cys Gln Gly Lys Trp Asp Leu Leu Thr Lys Gln Cys Leu Lys
1 5 10 15

Leu Arg

<210> 165
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 165

Leu Met Trp Phe Trp Lys Trp Asp Leu Leu Thr Lys Gln Leu Val Pro
1 5 10 15

Thr Phe

<210> 166
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 166

Gln Thr Trp Ala Trp Lys Trp Asp Leu Leu Thr Lys Gln Trp Ile Gly
1 5 10 15

Pro Met

<210> 167
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 167

Asn Lys Glu Leu Leu Lys Trp Asp Leu Leu Thr Lys Gln Cys Arg Gly
1 5 10 15

Arg Ser

<210> 168
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 168

Gly Gln Lys Asp Leu Lys Trp Asp Leu Leu Thr Lys Gln Tyr Val Arg
1 5 10 15

Gln Ser

<210> 169
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 169

Pro Lys Pro Cys Gln Lys Trp Asp Leu Leu Thr Lys Gln Cys Leu Gly
1 5 10 15

Ser Val

<210> 170
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 170

Gly Gln Ile Gly Trp Lys Trp Asp Leu Leu Thr Lys Gln Trp Ile Gln
1 5 10 15

Thr Arg

<210> 171
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 171

Val Trp Leu Asp Trp Lys Trp Asp Leu Leu Thr Lys Gln Trp Ile His
1 5 10 15

Pro Gln

<210> 172
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 172

Gln Glu Trp Glu Tyr Lys Trp Asp Leu Leu Thr Lys Gln Trp Gly Trp
1 5 10 15

Leu Arg

<210> 173
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 173

His Trp Asp Ser Trp Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Val
1 5 10 15

Gln Ala

<210> 174
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 174

Thr Arg Pro Leu Gln Lys Trp Asp Leu Leu Thr Lys Gln Trp Leu Arg
1 5 10 15

Val Gly

<210> 175
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 175

Ser Asp Gln Trp Gln Lys Trp Asp Leu Leu Thr Lys Gln Trp Phe Trp
1 5 10 15

Asp Val

<210> 176
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 176

Gln Gln Thr Phe Met Lys Trp Asp Leu Leu Thr Lys Gln Trp Ile Arg
1 5 10 15

Arg His

<210> 177
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
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<400> 177

Gln Gly Glu Cys Arg Lys Trp Asp Leu Leu Thr Lys Gln Cys Phe Pro
1 5 10 15

Gly Gln

<210> 178

<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 178

Gly Gln Met Gly Trp Arg Trp Asp Pro Leu Ile Lys Met Cys Leu Gly
1 5 10 15

Pro Ser

<210> 179
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 179

Gln Leu Asp Gly Cys Lys Trp Asp Leu Leu Thr Lys Gln Lys Val Cys
1 5 10 15

Ile Pro

<210> 180
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 180

His Gly Tyr Trp Gln Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Ser
1 5 10 15

Ser Glu

<210> 181
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 181

His Gln Gly Gln Cys Gly Trp Asp Leu Leu Thr Arg Ile Tyr Leu Pro
1 5 10 15

Cys His

<210> 182
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 182

Leu His Lys Ala Cys Lys Trp Asp Leu Leu Thr Lys Gln Cys Trp Pro
1 5 10 15

Met Gln

<210> 183
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 183

Gly Pro Pro Gly Ser Val Trp Asp Leu Leu Thr Lys Ile Trp Ile Gln
1 5 10 15

Thr Gly

<210> 184
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 184

Ile Thr Gln Asp Trp Arg Phe Asp Thr Leu Thr Arg Leu Trp Leu Pro
1 5 10 15

Leu Arg

<210> 185
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 185

Gln Gly Gly Phe Ala Ala Trp Asp Val Leu Thr Lys Met Trp Ile Thr

1 5 10 15

Val Pro

<210> 186
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 186

Gly His Gly Thr Pro Trp Trp Asp Ala Leu Thr Arg Ile Trp Ile Leu
1 5 10 15

Gly Val

<210> 187
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 187

Val Trp Pro Trp Gln Lys Trp Asp Leu Leu Thr Lys Gln Phe Val Phe
1 5 10 15

Gln Asp

<210> 188
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred TALL-1 modulating domains

<400> 188

Trp Gln Gln Trp Ser Trp Lys Trp Asp Leu Leu Thr Arg Gln Tyr Ile
1 5 10 15

Ser Ser Ser

<210> 189
<211> 882
<212> DNA
<213> Artificial Sequence

<220>
<223> TALL-1 12-3 tandem dimer

<400> 189
atgcttccag gctgcaagtg ggatcttctt attaagcaat gggtatgcga tccacttgga 60

tccggttctg ctactggtgg ttccggctcc accgcaagct ctggttcagg cagtgcgact 120

catatgctgc cgggttgtaa atgggacctg ctgatcaaac agtgggtttg tgacccgctg 180

ggtggaggcg gtggggtcga caaaactcac acatgtccac cttgtccagc tccggaactc 240

ctgggggggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc 300

cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 360

ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 420

cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 480

aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa 540

accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc 600

cgggatgagc tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc 660

agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 720

cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag 780

agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 840

cactacacgc agaagagcct ctccctgtct ccgggtaaat aa 882

<210> 190
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred linker

<400> 190

Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly
1 5 10 15

Ser Gly Ser Ala Thr Gly Met
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<210> 191
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Preferred linker

<400> 191

Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly
1 5 10 15

Ser Gly Ser Ala Thr Gly Ser
20

Ser Gly Ser Ala Thr Xaa Xaa Gly Ser Gly Ser Ala Thr Gly Gly Ser
20 25 30

Gly Ser Thr Ala Ser Ser Gly Ser Gly Ser Ala Thr Xaa Xaa
35 40 45

<210> 195
<211> 38
<212> PRT
<213> Human

<400> 195

Met Arg Arg Gly Pro Arg Ser Leu Arg Gly Arg Asp Ala Pro Val Pro
1 5 10 15

Thr Pro Cys Val Pro Thr Glu Cys Tyr Asp Leu Leu Val Arg Lys Cys
20 25 30

Val Asp Cys Arg Leu Leu
35

<210> 196
<211> 41
<212> PRT
<213> Human

<400> 196

Thr Ile Cys Asn His Gln Ser Gln Arg Thr Cys Ala Ala Phe Cys Arg
1 5 10 15

Ser Leu Ser Cys Arg Lys Glu Gln Gly Lys Phe Tyr Asp His Leu Leu
20 25 30

Arg Asp Cys Ile Ser Cys Ala Ser Ile
35 40

<210> 197
<211> 42
<212> PRT
<213> Human

<400> 197

Phe Val Ser Pro Ser Gln Glu Ile Arg Gly Arg Phe Arg Arg Met Leu
1 5 10 15

Gln Met Ala Gly Gln Cys Ser Gln Asn Glu Tyr Phe Asp Ser Leu Leu
20 25 30

His Ala Cys Ile Pro Cys Gln Leu Arg Cys
35 40

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(74) Agents: ODRE, Steven et al.; Amgen, Inc., One Amgen Center Drive, M/S 27-4-A, Thousand Oaks, CA 91320-1799 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

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[Continued on next page]

(54) Title: PEPTIDES AND RELATED MOLECULES THAT BIND TO TALL-1

$a^1a^2a^3CDa^6La^8a^9a^{10}Ca^{12}a^{13}a^{14}$

(SEQ. ID. NO: 100),

$b^1b^2b^3Cb^5b^6Db^8Lb^{10}b^{11}b^{12}b^{13}b^{14}Cb^{16}b^{17}b^{18}$

(SEQ. ID. NO: 104)

$c^1c^2c^3Cc^5Dc^7Lc^9c^{10}c^{11}c^{12}c^{13}c^{14}Cc^{16}c^{17}c^{18}$

(SEQ. ID. NO: 105)

$d^1d^2d^3Cd^5d^6d^7WDd^{10}Ld^{13}d^{14}d^{15}Cd^{16}d^{17}d^{18}$

(SEQ. ID. NO: 106)

$e^1e^2e^3Ce^5e^6e^7De^9Le^{11}Ke^{13}Ce^{15}e^{16}e^{17}e^{18}$

(SEQ. ID. NO: 107)

$f^1f^2f^3Kf^5Df^7Lf^9f^{10}Qf^{12}f^{13}f^{14}$

(SEQ. ID NO: 109)

$(X^1)_a$-V^1-$(X^2)_b$ (I)

(57) Abstract: The present invention concerns therapeutic agents that modulate the activity of TALL-1. In accordance with the present invention, modulators of TALL-1 may comprise an amino acid sequence Dz^2Lz^4 wherein z^2 is an amino acid residue and z^4 is threonyl or isoleucyl. Exemplary molecules comprise a sequence of the formulae $a^1a^2a^3CDa^6La^8a^9a^{10}Ca^{12}a^{13}a^{14}$ (SEQ.ID.NO:100), $b^1b^2b^3Cb^5b^6Db^8Lb^{10}b^{11}b^{12}b^{13}b^{14}Cb^{16}b^{17}b^{18}$ (SEQ.ID.NO:104) $c^1c^2c^3Cc^5Dc^7Lc^9c^{10}c^{11}c^{12}c^{13}c^{14}Cc^{16}c^{17}c^{18}$ (SEQ.ID.NO:105) $d^1d^2d^3Cd^5d^6d^7WDd^{10}Ld^{13}d^{14}d^{15}Cd^{16}d^{17}d^{18}$ (SEQ.ID.NO:106) $e^1e^2e^3Ce^5e^6e^7De^9Le^{11}Ke^{13}Ce^{15}e^{16}e^{17}e^{18}$ (SEQ.ID.NO:107) $f^1f^2f^3Kf^5Df^7Lf^9f^{10}Qf^{12}f^{13}f^{14}$ (SEQ.ID NO:109) wherein the substituents are as defined in the specification. The invention further comprises compositions of matter of the formula $(X^1)_a$-V^1-$(X^2)_b$ wherein V^1 is a vehicle that is covalently attached to one or more of the above TALL-1 modulating compositions of matter. The vehicle and the TALL-1 modulating composition of matter may be linked through the N- or C-terminus of the TALL-1 modulating portion. The preferred vehicle is an Fc domain, and the preferred Fc domain is an IgG Fc domain.

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INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07K 14/52, 14/525; A61K 38/19; C12N 5/10, 15/28
US CL : 530/351, 402; 514/2, 8, 12; 536/23.5; 435/69.1, 71.1, 471, 320.1, 325, 252.3, 254.11
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 530/351, 402; 514/2, 8, 12; 536/23.5; 435/69.1, 71.1, 471, 320.1, 325, 252.3, 254.11

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Database PNAS, SHU, H.-B. et al. B cell maturation protein is a receptor for the tumor necrosis factor family member TALL-1. Proc. Natl. Acad. Sci. USA. 01 August 2000, Vol. 97, No. 16, pages 9156-9161.	1-62
A	Database PNAS, KHARE et al. Severe B cell hyperplasia and autoimmune disease in TALL-1 transgenis mice. Proc. Natl. Acad. Sci. USA. 28 March 2000, Vol. 97, No. 7, pages 3370-3375.	1-62

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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[Continued on next page]

(54) Title: PEPTIDES AND RELATED MOLECULES THAT BIND TO TALL-1

$a^1a^2a^3CDa^6La^8a^9a^{10}Ca^{12}a^{13}a^{14}$

(SEQ. ID. NO: 100),

$b^1b^2b^3Cb^5b^6Db^8Lb^{10}b^{11}b^{12}b^{13}b^{14}Cb^{16}b^{17}b^{18}$

(SEQ. ID. NO: 104)

$c^1c^2c^3Cc^5Dc^7Lc^9c^{10}c^{11}c^{12}c^{13}c^{14}Cc^{16}c^{17}c^{18}$

(SEQ. ID. NO: 105)

$d^1d^2d^3Cd^5d^6d^7WDd^{10}Ld^{13}d^{14}d^{15}Cd^{16}d^{17}d^{18}$

(SEQ. ID. NO: 106)

$e^1e^2e^3Ce^5e^6e^7De^9Le^{11}Ke^{13}Ce^{15}e^{16}e^{17}e^{18}$

(SEQ. ID. NO: 107)

$f^1f^2f^3Kf^5Df^7Lf^9f^{10}Qf^{12}f^{13}f^{14}$

(SEQ. ID NO: 109)

$(X^1)_a$-V^1-$(X^2)_b$ (I)

(57) Abstract: The present invention concerns therapeutic agents that modulate the activity of TALL-1. In accordance with the present invention, modulators of TALL-1 may comprise an amino acid sequence Dz^2Lz^4 wherein z^2 is an amino acid residue and z^4 is threonyl or isoleucyl. Exemplary molecules comprise a sequence of the formulae $a^1a^2a^3CDa^6La^8a^9a^{10}Ca^{12}a^{13}a^{14}$ (SEQ.ID.NO:100), $b^1b^2b^3Cb^5b^6Db^8Lb^{10}b^{11}b^{12}b^{13}b^{14}Cb^{16}b^{17}b^{18}$ (SEQ.ID.NO:104) $c^1c^2c^3Cc^5Dc^7Lc^9c^{10}c^{11}c^{12}c^{13}c^{14}Cc^{16}c^{17}c^{18}$ (SEQ.ID.NO:105) $d^1d^2d^3Cd^5d^6d^7WDd^{10}Ld^{13}d^{14}d^{15}Cd^{16}d^{17}d^{18}$ (SEQ.ID.NO:106) $e^1e^2e^3Ce^5e^6e^7De^9Le^{11}Ke^{13}Ce^{15}e^{16}e^{17}e^{18}$ (SEQ.ID.NO:107) $f^1f^2f^3Kf^5Df^7Lf^9f^{10}Qf^{12}f^{13}f^{14}$ (SEQ.ID NO:109) wherein the substituents are as defined in the specification. The invention further comprises compositions of matter of the formula $(X^1)_a$-V^1-$(X^2)_b$ wherein V^1 is a vehicle that is covalently attached to one or more of the above TALL-1 modulating compositions of matter. The vehicle and the TALL-1 modulating composition of matter may be linked through the N- or C-terminus of the TALL-1 modulating portion. The preferred vehicle is an Fc domain, and the preferred Fc domain is an IgG Fc domain.

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PEPTIDES AND RELATED MOLECULES THAT BIND TO TALL-1

This application is related to U.S. provisional application no. 60/290,196, filed May 11, 2001, which is hereby incorporated by reference.

Background of the Invention

After years of study in necrosis of tumors, tumor necrosis factors (TNFs) α and β were finally cloned in 1984. The ensuing years witnessed the emergence of a superfamily of TNF cytokines, including fas ligand (FasL), CD27 ligand (CD27L), CD30 ligand (CD30L), CD40 ligand (CD40L), TNF-related apoptosis-inducing ligand (TRAIL, also designated AGP-1), osteoprotegerin binding protein (OPG-BP or OPG ligand), 4-1BB ligand, LIGHT, APRIL, and TALL-1. Smith et al. (1994), Cell 76: 959-962; Lacey et al. (1998), Cell 93: 165-176; Chichepotiche et al. (1997), J. Biol. Chem. 272: 32401-32410; Mauri et al. (1998), Immunity 8: 21-30; Hahne et al. (1998), J. Exp. Med. 188: 1185-90; Shu et al. (1999), J. Leukocyte Biology 65: 680-3. This family is unified by its structure, particularly at the C-terminus. In addition, most members known to date are expressed in immune compartments, although some members are also expressed in other tissues or organs, as well. Smith et al. (1994), Cell 76: 959-62. All ligand members, with the exception of LT-α, are type II transmembrane proteins, characterized by a conserved 150 amino acid region within C-terminal extracellular domain. Though restricted to only 20-25% identity, the conserved 150 amino acid domain folds into a characteristic β-pleated sheet sandwich and trimerizes. This conserved region can be proteolytically released, thus generating a soluble functional form. Banner et al. (1993), Cell 73: 431-445.

Many members within this ligand family are expressed in lymphoid enriched tissues and play important roles in the immune system development and modulation. Smith et al. (1994). For example, TNFα is mainly synthesized by macrophages and is an important mediator for inflammatory responses and immune defenses. Tracey & Cerami (1994), Ann. Rev. Med. 45: 491-503. Fas-L, predominantly expressed in activated T cell, modulates TCR-mediated apoptosis of thymocytes. Nagata, S. & Suda, T. (1995) Immunology Today 16: 39-43; Castrim et al. (1996), Immunity 5: 617-27. CD40L, also expressed by activated T cells, provides an essential signal for B cell survival, proliferation and immunoglobulin isotype switching. Noelle (1996), Immunity 4: 415-9.

The cognate receptors for most of the TNF ligand family members have been identified. These receptors share characteristic multiple cysteine-rich repeats within their extracellular domains, and do not possess catalytic motifs within cytoplasmic regions. Smith et al. (1994). The receptors signal through direct interactions with death domain proteins (e.g. TRADD, FADD, and RIP) or with the TRAF proteins (e.g. TRAF2, TRAF3, TRAF5, and TRAF6), triggering divergent and overlapping signaling pathways, e.g. apoptosis, NF-κB activation, or JNK activation. Wallach et al. (1999), Annual Review of Immunology 17: 331-67. These signaling events lead to cell death, proliferation, activation or differentiation. The expression profile of each receptor member varies. For example, TNFR1 is expressed on a broad spectrum of tissues and cells, whereas the cell surface receptor of OPGL is mainly restricted to the osteoclasts. Hsu et al. (1999) Proc. Natl. Acad. Sci. USA 96: 3540-5.

A number of research groups have recently identified TNF family ligands with the same or substantially similar sequence. The ligand has been variously named neutrokine α (WO 98/18921, published May 7, 1998), 63954 (WO 98/27114, published June 25, 1998), TL5 (EP 869 180, published October 7, 1998), NTN-2 (WO 98/55620 and WO 98/55621,

published December 10, 1998), TNRL1-alpha (WO 9911791, published March 11, 1999), kay ligand (WO99/12964, published March 18, 1999), and AGP-3 (U.S. Prov. App. Nos. 60/119,906, filed February 12, 1999 and 60/166,271, filed November 18, 1999, respectively); and TALL-1 (WO 00/68378, published Nov. 16, 2000). Each of these references is hereby incorporated by reference. Hereinafter, the ligands reported therein are collectively referred to as TALL-1.

TALL-1 is a member of the TNF ligand superfamily that is functionally involved in B cell survival and proliferation. Transgenic mice overexpressing TALL-1 had severe B cell hyperplasia and lupus-like autoimmune disease. Khare et al. (2000) PNAS 97(7):3370-3375). Both TACI and BCMA serve as cell surface receptors for TALL-1. Gross et al. (2000), Nature **404**: 995-999; Ware (2000), J. Exp. Med. **192**(11): F35-F37; Ware (2000), Nature **404**: 949-950; Xia et al. (2000), J. Exp. Med. **192**(1):137-143; Yu et al. (2000), Nature Immunology **1**(3):252-256; Marsters et al. (2000), Current Biology **10**:785-788; Hatzoglou et al. (2000) J. of Immunology **165**:1322-1330; Shu et al. (2000) PNAS **97**(16):9156-9161; Thompson et al. (2000) J. Exp. Med. **192**(1):129-135; Mukhopadhyay et al. (1999) J. Biol. Chem. **274**(23): 15978-81; Shu et al. (1999) J. Leukocyte Biol. **65**:680-683; Gruss et al. (1995) Blood **85**(12): 3378-3404; Smith et al. (1994), Cell **76**: 959-962; U.S. Pat. No. 5,969,102, issued October 19, 1999; WO 00/67034, published November 9, 2000; WO 00/40716, published July 13, 2000; WO 99/35170, published July 15, 1999. Both receptors are expressed on B cells and signal through interaction with TRAF proteins. In addition, both TACI and BCMA also bind to another TNF ligand family member, APRIL. Yu et al. (2000), Nature Immunology 1(3) :252-256. APRIL has also been demonstrated to induce B cell proliferation.

To date, no recombinant or modified proteins employing peptide modulators of TALL-1 have been disclosed. Recombinant and modified

proteins are an emerging class of therapeutic agents. Useful modifications of protein therapeutic agents include combination with the "Fc" domain of an antibody and linkage to polymers such as polyethylene glycol (PEG) and dextran. Such modifications are discussed in detail in a patent application entitled, "Modified Peptides as Therapeutic Agents," publicshed WO 00/24782, which is hereby incorporated by reference in its entirety.

A much different approach to development of therapeutic agents is peptide library screening. The interaction of a protein ligand with its receptor often takes place at a relatively large interface. However, as demonstrated for human growth hormone and its receptor, only a few key residues at the interface contribute to most of the binding energy. Clackson et al. (1995), Science 267: 383-6. The bulk of the protein ligand merely displays the binding epitopes in the right topology or serves functions unrelated to binding. Thus, molecules of only "peptide" length (2 to 40 amino acids) can bind to the receptor protein of a given large protein ligand. Such peptides may mimic the bioactivity of the large protein ligand ("peptide agonists") or, through competitive binding, inhibit the bioactivity of the large protein ligand ("peptide antagonists").

Phage display peptide libraries have emerged as a powerful method in identifying such peptide agonists and antagonists. See, for example, Scott et al. (1990), Science 249: 386; Devlin et al. (1990), Science 249: 404; U.S. Pat. No. 5,223,409, issued June 29, 1993; U.S. Pat. No. 5,733,731, issued March 31, 1998; U.S. Pat. No. 5,498,530, issued March 12, 1996; U.S. Pat. No. 5,432,018, issued July 11, 1995; U.S. Pat. No. 5,338,665, issued August 16, 1994; U.S. Pat. No. 5,922,545, issued July 13, 1999; WO 96/40987, published December 19, 1996; and WO 98/15833, published April 16, 1998 (each of which is incorporated by reference in its entirety). In such libraries, random peptide sequences are displayed by fusion with

coat proteins of filamentous phage. Typically, the displayed peptides are affinity-eluted against an immobilized target protein. The retained phages may be enriched by successive rounds of affinity purification and repropagation. The best binding peptides may be sequenced to identify key residues within one or more structurally related families of peptides. See, e.g., Cwirla et al. (1997), Science 276: 1696-9, in which two distinct families were identified. The peptide sequences may also suggest which residues may be safely replaced by alanine scanning or by mutagenesis at the DNA level. Mutagenesis libraries may be created and screened to further optimize the sequence of the best binders. Lowman (1997), Ann. Rev. Biophys. Biomol. Struct. 26: 401-24.

Structural analysis of protein-protein interaction may also be used to suggest peptides that mimic the binding activity of large protein ligands. In such an analysis, the crystal structure may suggest the identity and relative orientation of critical residues of the large protein ligand, from which a peptide may be designed. See, e.g., Takasaki et al. (1997), Nature Biotech. 15: 1266-70. These analytical methods may also be used to investigate the interaction between a receptor protein and peptides selected by phage display, which may suggest further modification of the peptides to increase binding affinity.

Other methods compete with phage display in peptide research. A peptide library can be fused to the carboxyl terminus of the lac repressor and expressed in E. coli. Another E. coli-based method allows display on the cell's outer membrane by fusion with a peptidoglycan-associated lipoprotein (PAL). Hereinafter, these and related methods are collectively referred to as "E. coli display." In another method, translation of random RNA is halted prior to ribosome release, resulting in a library of polypeptides with their associated RNA still attached. Hereinafter, this and related methods are collectively referred to as "ribosome display."

Other methods employ peptides linked to RNA; for example, PROfusion technology, Phylos, Inc. See, for example, Roberts & Szostak (1997), Proc. Natl. Acad. Sci. USA, 94: 12297-303. Hereinafter, this and related methods are collectively referred to as "RNA-peptide screening." Chemically derived peptide libraries have been developed in which peptides are immobilized on stable, non-biological materials, such as polyethylene rods or solvent-permeable resins. Another chemically derived peptide library uses photolithography to scan peptides immobilized on glass slides. Hereinafter, these and related methods are collectively referred to as "chemical-peptide screening." Chemical-peptide screening may be advantageous in that it allows use of D-amino acids and other unnatural analogues, as well as non-peptide elements. Both biological and chemical methods are reviewed in Wells & Lowman (1992), Curr. Opin. Biotechnol. 3: 355-62. Conceptually, one may discover peptide mimetics of any protein using phage display, RNA-peptide screening, and the other methods mentioned above.

Summary of the Invention

The present invention concerns therapeutic agents that modulate the activity of TALL-1. In accordance with the present invention, modulators of TALL-1 may comprise an amino acid sequence Dz^2Lz^4 (SEQ ID NO: 108) wherein z^2 is an amino acid residue and z^4 is threonyl or isoleucyl. Such modulators of TALL-1 comprise molecules of the following formulae:

I(a) $a^1a^2a^3CDa^6La^8a^9a^{10}Ca^{12}a^{13}a^{14}$

(SEQ. ID. NO: 100)

wherein:

a^1, a^2, a^3 are each independently absent or amino acid residues;

a^6 is an amino acid residue;

a^9 is a basic or hydrophobic residue;

a^8 is threonyl or isoleucyl;